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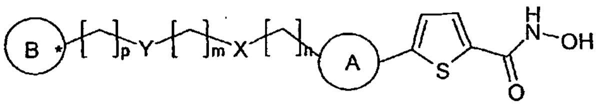
(54) Title: SUBSTITUTED THIENYL-HYDROXAMIC ACIDS HAVING HISTONE DEACETYLASE ACTIVITY



(I)

(57) **Abstract:** A compound of formula (I): in which A represents optionally substituted monocyclic heteroaryl or phenyl B represents optionally substituted heteroaryl, aryl, aryl-fused-heterocycloalkyl, heteroaryl-fused-cycloalkyl, heteroaryl-fused-heterocycloalkyl or aryl-fused-cycloalkyl X and Y, which may be the same or different, each independently represent -0-, -NR^1-, CO-, -S0$_2$-, -SO-, -S-, -NR^{1}CO-, -NR^{1}S0$_2$-, -CONR^1-, -SO$_2$NR^1-, -NR^{1}CONR^1 or X may be a direct bond when Y represents -NR^1-, -NR^{1}CO-, -NR^{1}SO$_2$-, -CONR^1-, - SO$_2$NR^1- or -NR^{1}CONR^1- provided that R^1 represents alkyl substituted by -OR^2, -NR^{3}R^4, - NR^{4}COR^5, -NR^{4}SO$_2$R^5, -CONR^{3}R^4 or -S0$_2$NR^{3}R^4 R^1 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, or alkyl substituted by -OR^2, -NR^{3}R^4, -NR^{4}COR^5, -NR^{4}S0$_2$R^5, -CONR^{3}R^4 or -S0$_2$NR^{3}R^4 R^2 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl R^3 represents H or alkyl R^4 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl or NR^{3}R^4 represents a cyclic amine R^5 represents alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl n represents 0-3 m represents 1-3 p represents 0-3 and corresponding *N*-oxides, pharmaceutically acceptable salts, solvates and prodrugs thereof; and use to treat a disease in which inhibition of histone deacetylase can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease.

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SUBSTITUTED THIENYL-HYDROXAMIC ACIDS HAVING HISTONE DEACETYLASE ACTIVITY

This invention relates to substituted thienyl-hydroxamic acids, their preparation and pharmaceutical compositions containing these compounds for treating diseases associated with histone deacetylase enzymatic activity.

In eukaryotic cells, DNA is tightly associated with histones to form a compact complex called chromatin. The histones, generally highly conserved across eukaryotic species, constitute a family of proteins which are rich in basic amino acids that contact the phosphate groups of DNA.

There are different types of histones, including H1, H2A, H2B, H3 and H4. Four pairs of each of H2A, H2B, H3 and H4 together form a disk-shaped octomeric protein core, around which DNA is wound (with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA) to form a nucleosome. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

Histone deacetylases (HDACs) are part of transcriptional corepressor complexes and play key roles in regulating chromatin structure. Three different classes of human HDACs have been defined based on their homology to HDACs found in *Saccharomyces cerevisiae*. Class I HDACs (HDAC1, 2, 3, and 8) are related to the yeast transcriptional regulator RPD3. Class II HDACs (HDAC4, 5, 6, 7, 9, and 10) are similar to HDA1, another deacetylase in yeast. Class III HDACs are related to the yeast silencing protein SIR2 and are dependent on NAD for enzymatic activity.

Reversible acetylation of histones is a major regulator of gene expression that acts by altering accessibility of transcription factors to DNA. In normal cells, histone deacetylase (HDAC) and histone acetyltransferases (HATs) together control the level of acetylation of histones to maintain a balance. Histone acetylation has a key role in transcriptional activation, whereas deacetylation of histones correlates with the transcriptional repression and silencing of genes [for a review of histone deacetylation see Kouzarides *Curr. Opin.*

Genet. Dev., 9:40-48 (1999); Johnstone RW *Nat. Rev. Drug Discov.*, 1:287-299 (2002)]. Genetic repression may have an important role in neuronal ageing, atrophy and degenerative diseases.

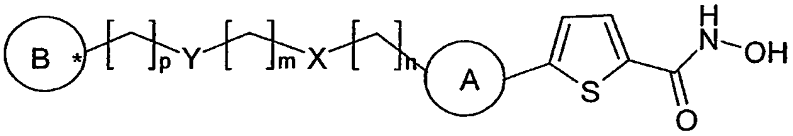
Moreover, histone deacetylases have been shown to regulate the activity of non-histone proteins through the modification of their acetylation level. These include steroid receptors such as estrogen and androgen receptors [Wang *et al*, *J. Biol. Chem.*, 276:18375-83 (2001), Gaughan *et al*, *J. Biol. Chem.*, 277: 25904-13 (2002)], transcription factors such as p53, E2F and myoD [Luo *et al*, *Nature*, 408:377-381 (2000); Ito *et al*, *EMBO J*, 19:1176-1179 (2001); Sartorelli *et al*, *Mol. Cell*, 4:725-734 (1999)], and cytoplasmic proteins such as α-tubulin [Hubbert *et al*, *Nature*, 417:455-458 (2002)].

There are currently several known inhibitors, both natural and synthetic, of HDAC. Some natural inhibitors include: (i) trapoxin B; (ii) trichostatin A [Yoshida and Beppu, *Exper. Cell Res.*, 177:122-131 (1988)]; and (iii) chlamydocin. Synthetic inhibitors include suberoyl anilide hydroxamic acid [Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, 95: 3003-3007 (1998)] and phenylbutyrate [Johnstone RW *Nat. Rev. Drug Discov.*, 1:287-299 (2002)].

Trichostatin A has been shown to cause arrest of rat fibroblasts at both G_1 and G_2 phases of the cell cycle, implicating HDAC in cell cycle regulation [Yoshida and Beppu, *Exper. Cell Res.*, 177:122-131 (1988)]. Trichostatin A and suberoyl anilide hydroxamic acid have been shown to inhibit cell growth, induce terminal differentiation and prevent the formation of tumors in mice [Johnstone RW *Nat. Rev. Drug Discov.*, 1:287-299 (2002)]. Trapoxin, trichostatin, and depudecin have been used to study gene regulation by HDAC-mediated chromatin remodeling [Christian A. Hassig, Stuart L. Schreiber, *Curr. Opinion in Chem. Biol.*, 1997, 1, 300-308; Christian A. Hassig, Jeffrey K. Tong, Stuart L. Schreiber, *Chem. & Biol.*, 1997, 4, 783-789; Christian A. Hassig, Jeffrey K. Tong, Tracey C. Fleischer, Takashi Owa, Phyllis Grable, Donald E. Ayer, Stuart L. Schreiber, *Proc. Natl. Acad. Sci., U.S.A.*, 1998, 95, 3519-3524; Ho Jeong Kwon, Takashi Owa, Christian A. Hassig, Junichi Shimada, Stuart L. Schreiber, *Proc. Natl. Acad. Sci., U.S.A.* 1998, 95, 3356-3361].

It is an objective of the present invention to provide inhibitors of histone deacetylase.

Thus, in one aspect, the present invention provides compounds of formula (I):



(I)

in which

A represents optionally substituted monocyclic heteroaryl or phenyl

B represents optionally substituted heteroaryl, aryl, aryl-fused-heterocycloalkyl, heteroaryl-fused-cycloalkyl, heteroaryl-fused-heterocycloalkyl or aryl-fused-cycloalkyl

X and Y, which may be the same or different, each independently represent -O-, $-NR^1-$, -CO-, $-SO_2-$, -SO-, -S-, $-NR^1CO-$, $-NR^1SO_2-$, $-CONR^1-$, $-SO_2NR^1-$, $-NR^1CONR^1-$ or X may be a direct bond when Y represents $-NR^1-$, $-NR^1CO-$, $-NR^1SO_2-$, $-CONR^1-$, $-SO_2NR^1-$ or $-NR^1CONR^1-$ provided that R^1 represents alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$

R^1 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, or alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$

R^2 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl

R^3 represents H or alkyl

R^4 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl

or NR^3R^4 represents a cyclic amine

R^5 represents alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl

n represents 0-3
m represents 1-3
p represents 0-3

and corresponding *N*-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compounds.

A second aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof, in admixture with a pharmaceutically acceptable carrier or excipient.

A third aspect of the invention is a compound of formula (I) or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof for use in therapy.

A fourth aspect of the invention is the use of a compound of formula (I), or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof, in the manufacture of a medicament for the treatment of a disease in which inhibition of histone deacetylase can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease.

A fifth aspect of the invention is a method for treating a disease in a patient in which inhibition of histone deacetylase can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the patient a therapeutically effective amount of compound of formula (I) or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof.

A sixth aspect of the invention is a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with a compound of formula (I) or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof.

A seventh aspect of the invention is a method of preparing a compound of formula (I) or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof.

An eighth aspect of the invention is a method of making a pharmaceutical composition comprising combining a compound of formula (I), or an *N*-oxide, pharmaceutically acceptable salt, solvate or prodrug thereof, with a pharmaceutically acceptable carrier or excipient.

For purposes of the present invention, the following definitions as used throughout the description of the invention shall be understood to have the following meanings:

"Compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula (I) as hereinbefore described, their *N*-oxides, their prodrugs, their pharmaceutically acceptable salts and their solvates, where the context so permits.

"Histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from lysine residues of proteins including, but not limited to, histones, transcription factors, steroid receptors and tubulin. Unless otherwise indicated the term histone is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4 and H5 from any species. In one preferred embodiment the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, and HDAC-10. In another preferred embodiment the histone deacetylase is derived from a protozoal or fungal source.

"Patient" includes both human and other mammals.

For purposes of the present invention, the following chemical terms as used above, and throughout the description of the invention, and unless otherwise indicated, shall be understood to have the following meanings:

"Acyl" means a -CO-alkyl group in which the alkyl group is as described herein. Exemplary acyl groups include $-COCH_3$ and $-COCH(CH_3)_2$.

“Acylamino” means a -NR-acyl group in which R and acyl are as described herein. Exemplary acylamino groups include -$NHCOCH_3$ and -$N(CH_3)COCH_3$.

“Alkoxy” and “alkyloxy” means an -O-alkyl group in which alkyl is as defined below. Exemplary alkoxy groups include methoxy and ethoxy.

“Alkoxycarbonyl” means a -COO-alkyl group in which alkyl is as defined below. Exemplary alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl.

“Alkyl” as a group or part of a group refers to a straight or branched chain saturated hydrocarbon group having from 1 to 12, preferably 1 to 6, carbon atoms, in the chain. Exemplary alkyl groups include methyl, ethyl, 1-propyl and 2-propyl.

“Alkylamino” means a -NH-alkyl group in which alkyl is as defined above. Exemplary alkylamino groups include methylamino and ethylamino.

“Alkylsufinyl” means a -SO-alkyl group in which alkyl is as defined above. Exemplary alkylsulfinyl groups include methylsulfinyl and ethylsulfinyl.

“Alkylsufonyl” means a -SO_2-alkyl group in which alkyl is as defined above. Exemplary alkylsulfonyl groups include methylsulfonyl and ethylsulfonyl.

“Alkylthio” means a -S-alkyl group in which alkyl is as defined above. Exemplary alkylthio groups include methylthio and ethylthio.

“Aminoacyl” means a -CO-NRR group in which R is as herein described. Exemplary aminoacyl groups include -$CONH_2$ and -$CONHCH_3$.

“Aminoalkyl” means an alkyl-NH_2 group in which alkyl is as previously described. Exemplary aminoalkyl groups include –CH_2NH_2.

"Aminosulfonyl" means a $-SO_2-NRR$ group in which R is as herein described. Exemplary aminosulfonyl groups include $-SO_2NH_2$ and $-SO_2NHCH_3$.

"Aryl" as a group or part of a group denotes an optionally substituted monocyclic or multicyclic (particularly bicyclic) aromatic carbocyclic moiety of from 6 to 14 carbon atoms, preferably from 6 to 10 carbon atoms, such as phenyl or naphthyl, and in one embodiment preferably phenyl. The aryl group may be substituted by one or more substituent groups.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C_{1-4} alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl and naphthlenemethyl.

"Arylalkyloxy" means an aryl-alkyloxy- group in which the aryl and alkyloxy moieties are as previously described. Preferred arylalkyloxy groups contain a C_{1-4} alkyl moiety. Exemplary arylalkyl groups include benzyloxy.

"Aryl-fused-cycloalkyl" means a monocyclic aryl ring, such as phenyl, fused to a cycloalkyl group, in which the aryl and cycloalkyl are as described herein. Exemplary aryl-fused-cycloalkyl groups include tetrahydronaphthyl and indanyl. The aryl and cycloalkyl rings may each be substituted by one or more substituent groups. The aryl-fused-cycloalkyl group may be attached to the remainder of the compound of formula (I) by any available carbon atom.

"Aryl-fused-heterocycloalkyl" means a monocyclic aryl ring, such as phenyl, fused to a heterocycloalkyl group, in which the aryl and heterocycloalkyl are as described herein. Exemplary aryl-fused-heterocycloalkyl groups include tetrahydroquinolinyl, indolinyl, benzodioxinyl, benzodioxolyl, dihydrobenzofuranyl and isoindolonyl. The aryl and heterocycloalkyl rings may each be substituted by one or more substituent groups. The aryl-fused-heterocycloalkyl group may be attached to the remainder of the compound of formula (I) by any available carbon or nitrogen atom.

"Aryloxy" means an -O-aryl group in which aryl is described above. Exemplary aryloxy groups include phenoxy.

"Cyclic amine" means an optionally substituted 3 to 8 membered monocyclic cycloalkyl ring system where one of the ring carbon atoms is replaced by nitrogen, and which may optionally contain an additional heteroatom selected from O, S or NR (where R is as described herein). Exemplary cyclic amines include pyrrolidine, piperidine, morpholine, piperazine and *N*-methylpiperazine. The cyclic amine group may be substituted by one or more substituent groups.

"Cycloalkyl" means an optionally substituted saturated monocyclic or bicyclic ring system of from 3 to 12 carbon atoms, preferably from 3 to 8 carbon atoms, and more preferably from 3 to 6 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl group may be substituted by one or more substituent groups.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocyclic cycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Dialkylamino" means a -N(alkyl)$_2$ group in which alkyl is as defined above. Exemplary dialkylamino groups include dimethylamino and diethylamino.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro or chloro.

"Haloalkoxy" means an -O-alkyl group in which the alkyl is substituted by one or more halogen atoms. Exemplary haloalkyl groups include trifluoromethoxy and difluoromethoxy.

"Haloalkyl" means an alkyl group which is substituted by one or more halo atoms. Exemplary haloalkyl groups include trifluoromethyl.

"Heteroaryl" as a group or part of a group denotes an optionally substituted aromatic monocyclic or multicyclic organic moiety of from 5 to 14 ring atoms, preferably from 5 to

10 ring atoms, in which one or more of the ring atoms is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Examples of such groups include benzimidazolyl, benzoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups. The heteroaryl group may be substituted by one or more substituent groups. The heteroaryl group may be attached to the remainder of the compound of formula (I) by any available carbon or nitrogen atom.

"Heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl.

"Heteroarylalkyloxy" means a heteroaryl-alkyloxy- group in which the heteroaryl and alkyloxy moieties are as previously described. Preferred heteroarylalkyloxy groups contain a lower alkyl moiety. Exemplary heteroarylalkyloxy groups include pyridylmethyloxy.

"Heteroaryloxy" means a heteroaryloxy- group in which the heteroaryl is as previously described. Exemplary heteroaryloxy groups include pyridyloxy.

"Heteroaryl-fused-cycloalkyl" means a monocyclic heteroaryl group, such as pyridyl or furanyl, fused to a cycloalkyl group, in which heteroaryl and cycloalkyl are as previously described. Exemplary heteroaryl-fused-cycloalkyl groups include tetrahydroquinolinyl and tetrahydrobenzofuranyl. The heteroaryl and cycloalkyl rings may each be substituted by one or more substituent groups. The heteroaryl-fused-cycloalkyl group may be attached to the remainder of the compound of formula (I) by any available carbon or nitrogen atom.

"Heteroaryl-fused-heterocycloalkyl" means a monocyclic heteroaryl group, such as pyridyl or furanyl, fused to a heterocycloalkyl group, in which heteroaryl and heterocycloalkyl are as previously described. Exemplary heteroaryl-fused-heterocycloalkyl groups include dihydrodioxinopyridinyl, dihydropyrrolopyridinyl, dihydrofuranopyridinyl and dioxolopyridinyl. The heteroaryl and heterocycloalkyl rings may each be substituted by one or more substituents groups. The heteroaryl-fused-heterocycloalkyl group may be attached to the remainder of the compound of formula (I) by any available carbon or nitrogen atom.

“Heterocycloalkyl” means: (i) an optionally substituted cycloalkyl group of from 4 to 8 ring members which contains one or more heteroatoms selected from O, S or NR; (ii) a cycloalkyl group of from 4 to 8 ring members which contains CONR and CONRCO (examples of such groups include 2-oxopyrrolidinyl and succinimidyl). The heterocycloalkyl group may be substituted by one or more substituent groups. The heterocycloalkyl group may be attached to the remainder of the compound of formula (I) by any available carbon or nitrogen atom.

“Heterocycloalkylalkyl” means a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as previously described.

“Lower alkyl” as a group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 4 carbon atoms in the chain, i.e. methyl, ethyl, propyl (^{n}propyl or ^{i}propyl) or butyl (^{n}butyl, ^{i}butyl or ^{t}butyl).

“R” means hydrogen, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkyl, heteroaryl or aryl.

“Sulfonyl” means a $-SO_2$-alkyl group in which alkyl is as described herein. Exemplary sulfonyl groups include methanesulfonyl.

“Sulfonylamino” means a -NR-sulfonyl group in which R and sulfonyl are as described herein. Exemplary sulfonylamino groups include $-NHSO_2CH_3$.

"Pharmaceutically acceptable salt" means a physiologically or toxicologically tolerable salt and include, when appropriate, pharmaceutically acceptable base addition salts and pharmaceutically acceptable acid addition salts. For example (i) where a compound of the invention contains one or more acidic groups, for example carboxy groups, pharmaceutically acceptable base addition salts that may be formed include sodium, potassium, calcium, magnesium and ammonium salts, or salts with organic amines, such as, diethylamine, *N*-methyl-glucamine, diethanolamine or amino acids (e.g. lysine) and the like; (ii) where a compound of the invention contains a basic group, such as an amino group, pharmaceutically acceptable acid addition salts that may be formed include hydrochlorides, hydrobromides, phosphates, acetates, citrates, lactates, tartrates, malonates, methanesulphonates and the like.

"Prodrug" means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) containing a hydroxy group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. As another example an ester prodrug of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis *in vivo* to the parent molecule [Examples of ester prodrugs are those described by F. J. Leinweber, Drug Metab. Res., 18:379 (1987)].

"Saturated" pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The cyclic groups referred to above, namely, aryl, heteroaryl, cycloalkyl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, heterocycloalkyl, aryl-fused-heterocycloalkyl, heteroaryl-fused-heterocycloalkyl and cyclic amine may be substituted by one or more substituent groups, and where substituted preferably one, two or three substituent groups are present, particularly one or two substituent groups. Suitable optional substituent groups include acyl (e.g. $-COCH_3$), alkoxy (e,g, $-OCH_3$), alkoxycarbonyl (e.g. $-COOCH_3$), alkylamino (e.g. $-NHCH_3$), alkylsulfinyl (e.g. $-SOCH_3$), alkylsulfonyl (e.g. $-SO_2CH_3$), alkylthio (e.g. $-SCH_3$), $-NH_2$, aminoalkyl (e.g. $-CH_2NH_2$), arylalkyl (e.g. $-CH_2Ph$ or $-CH_2-CH_2-Ph$), cyano, dialkylamino (e.g. $-N(CH_3)_2$), halo, haloalkoxy (e.g. $-OCF_3$ or

-$OCHF_2$), haloalkyl (e.g. -CF_3), alkyl (e.g. -CH_3 or -CH_2CH_3), -OH, -CHO, -NO_2, aryl (optionally substituted with alkoxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with alkoxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl, aminoacyl (e.g. -$CONH_2$, -$CONHCH_3$), aminosulfonyl (e.g. -SO_2NH_2, -SO_2NHCH_3), acylamino (e.g. -$NHCOCH_3$), sulfonylamino (e.g. -$NHSO_2CH_3$), heteroarylalkyl, cyclic amine (e.g. morpholine), aryloxy, heteroaryloxy, arylalkyloxy (e.g. benzyloxy) and heteroarylalkyloxy.

Compounds of the invention may exist in one or more geometrical, optical, enantiomeric, diastereomeric and tautomeric forms, including but not limited to *cis*- and *trans*-forms, *E*- and *Z*-forms, *R*-, *S*- and *meso*-forms, keto-, and enol-forms. Unless otherwise stated a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Where appropriate such isomers can be separated from their mixtures by the application or adaptation of known methods (e.g. chromatographic techniques and recrystallisation techniques). Where appropriate such isomers may be prepared by the application of adaptation of known methods (e.g. asymmetric synthesis).

With reference to formula (I) above, particular and preferred embodiments are described below.

In one embodiment, the group A is a monocyclic heteroaryl group, preferably containing 5 or 6 ring atoms. Preferably, the heteroatom(s) is/are selected from N, O and S atoms, and preferably from N atom(s). Preferably, there are one or two ring heteroatoms. In a preferred embodiment, A is selected from monocyclic heteroaryl groups containing 5 or 6 ring atoms including one or two nitrogen heteroatoms. Preferably, A is selected from pyrazolyl, imidazolyl, pyridinyl and pyrimidinyl. In one embodiment, A is selected from pyrazolyl, pyridinyl and pyrimidinyl. The group A may be substituted or unsubstituted, and in one embodiment, A is unsubstituted. In an alternative embodiment, A is substituted and in this embodiment one or two substituent groups may be present. The substituent groups are preferably selected from alkyl, alkoxy, haloalkyl, haloalkoxy, halogen and CN. In a preferred embodiment, A is selected from pyrazolyl, imidazolyl, pyridinyl and pyrimidinyl optionally substituted with a substituent chosen from alkyl, alkoxy, haloalkyl, haloalkoxy, halogen and CN.

R^1 is preferably selected from H, alkyl and alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$, particularly by $-OR^2$ or NR^3R^4. In an alternative embodiment, R^1 is selected from arylalkyl, heteroarylalkyl, heterocycloalkylalkyl and cycloalkylalkyl.

In one embodiment, R^2 is selected from H or alkyl. In one embodiment, R^4 is selected from H or alkyl. In one embodiment, R^5 is selected from alkyl.

In one embodiment, X and Y, which may be the same or different, each independently represent -O-, $-NR^1-$, -CO-, $-SO_2-$, $-NR^1CO-$, $-NR^1SO_2-$, $-CONR^1-$, $-SO_2NR^1-$, $-NR^1CONR^1-$, or X may be a direct bond when Y represents $-NR^1-$, $-NR^1CO-$, $-NR^1SO_2-$, $-CONR^1-$, $-SO_2NR^1-$ or $-NR^1CONR^1-$ provided that R^1 represents alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$.

In one embodiment, X is selected from -O- and $-NR^1-$, and particularly from $-NR^1-$. In this embodiment, R^1 is preferably selected from H, alkyl and alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$, particularly by $-OR^2$ or NR^3R^4, and particularly by $-OR^2$. Where R^1 is alkyl substituted by $-OR^2$, R^2 is particularly H or alkyl (preferably lower alkyl), and particularly H. Where R^1 is alkyl substituted by NR^3R^4, R^3 and R^4 are particularly H or alkyl, and particularly alkyl (preferably lower alkyl). In an alternative embodiment R^1 is selected from arylalkyl, heteroarylalkyl, heterocycloalkylalkyl and cycloalkylalkyl.

In a preferred embodiment, X is selected from -O- and -NH-.

In one embodiment, Y is selected from -O- and $-NR^1-$, and particularly from O. Where Y is selected from $-NR^1-$, R^1 is preferably selected from H, alkyl and alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$, particularly by $-OR^2$ or NR^3R^4. Where R^1 is alkyl substituted by $-OR^2$, R^2 is particularly H or alkyl (preferably lower alkyl), and particularly H. Where R^1 is alkyl substituted by NR^3R^4, R^3 and R^4 are particularly H or alkyl, and particularly alkyl (preferably lower alkyl). In an alternative embodiment R^1 is selected from arylalkyl, heteroarylalkyl, heterocycloalkylalkyl and cycloalkylalkyl. In a preferred embodiment, Y is selected from -O- and -NR^1- where R^1 is alkyl substituted by -OR^2 or NR^{3}R^4. In one embodiment, Y is selected from -O-.

Where X is a direct bond, then in one embodiment Y is -NR^1-, wherein R^1 is alkyl substituted by -OR^2, -NR^{3}R^4, -NR^{4}COR^5, -NR^{4}SO$_2$R^5, -CONR^{3}R^4 or -SO$_2$NR^{3}R^4

In one embodiment, the group B is selected from aryl and aryl-fused-heterocycloalkyl, preferably wherein said aryl is phenyl. The aryl may be optionally substituted, preferably by one or two substituent groups. Preferred substituent groups include halo, haloalkyl, alkoxy and acylamino.

In one embodiment, n is 0, 1 or 2; in a further embodiment n is 0 or 1; and in a further embodiment n is 1. Where A is pyrazolyl, then n is 2 or 3, particularly 2.

In one embodiment, m is 2 or 3. In an alternative embodiment, m is 1 or 2. In a further embodiment, m is 2.

In one embodiment, p is 0, 1 or 2; in a further embodiment p is 0 or 1; and in a further embodiment p is 0.

In one embodiment, A represents pyridinyl, n represents 0 or 1, X represents -NR^1-, m represents 2 or 3, Y represents -O- and p represents 0 or 1. Alternatively, n represents 1, Y represents -NR^1-, R^1 represents alkyl substituted by -NR^{3}R^4 or -OR^2, m represents 1, X is a direct bond and p represents 0 or 1, particularly 1.

In an alternative embodiment, A represents pyrazolyl, n represents 2, X represents -O-, m represents 2, Y represents -O- and p represents 0 or 1.

In an alternative embodiment, A represents imidazole.

In one embodiment compounds of the invention are:

5-[5-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide;

5-{1-[2-(2-phenoxy-ethoxy)-ethyl]-1*H*-pyrazol-3-yl}-thiophene-2-carboxylic acid hydroxyamide;
5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;
5-(6-{[3-(3-acetylamino-phenoxy)-propylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(6-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-{5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;
5-[6-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide;
and corresponding *N*-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compounds.

In another embodiment compounds of the invention are:
5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-3-yl}-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(3-trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(4-methoxy-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(2-chloro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(4-fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(3-methoxy-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(3-fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(2,6-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;
5-(5-{[2-(2,5-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2,6-dichloro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2,4-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{5-[(2-phenoxy-ethylamino)-methyl]-pyrimidin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[(2-hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

and corresponding *N*-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compounds.

In another embodiment compounds of the invention are:

5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{1-oxy-5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(4-trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(benzo[1,3]dioxol-5-yloxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[cyclopropylmethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[(2-hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[(2-hydroxy-ethyl)-phenethyl-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{5-[(2-phenoxy-ethylamino)-methyl]-1*H*-imidazol-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-{1-[2-(2-phenoxy-ethoxy)-ethyl]-1*H*-imidazol-4-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-1*H*-imidazol-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

and corresponding *N*-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compounds.

The present invention provides compounds that inhibit HDAC activity according to the tests described in the literature and in the Biological Activity section of this document. The therapeutic application of these compounds is pertinent to any disease that is known to be at least in part mediated by HDAC activity or whose symptoms are known to be alleviated by HDAC inhibitors (such as Trichostatin-A, suberoyl anilide hydroxamic acid, Trapoxin and depudecin). For example, these compounds could be beneficial for the treatment of cancer, psoriasis, fibroproliferative disorders (e.g. liver fibrosis), smooth muscle cell proliferation disorders (e.g. arteriosclerosis, restenosis), cardiomyocyte hypertrophy (e.g congestive heart failure), inflammatory diseases and conditions treatable by immune modulation (e.g. rheumatoid arthritis, autoimmune diabetes, lupus, allergies), neurodegenerative disorders (e.g. Huntington's disease), diseases involving angiogenesis (e.g. cancer, psoriasis, rheumatoid arthritis, retinal diseases such as diabetic retinopathy, age-related macular degeneration, interstitial keratitis, rubeotic glaucoma), fungal and parasitic infections (e.g. malaria, protozoal infections), haematopoietic disorders (e.g. anaemia, sickle cell anaemia, thalassemia) and conditions treatable by modulation of nuclear receptor activity (e.g. by increasing progesterone receptor activity to prevent premature parturition).

Thus, in one embodiment, the present invention is intended for the treatment of diseases caused by increased cell proliferation. These include, but are not limited to, primary and metastatic cancers of different origin (including those triggered by viral infections such as EBV, HIV, hepatitis B and C and KSHV), fibrosis of the liver, lung, kidney, heart and skin caused by myofibroblasts proliferation and increased production of extracellular matrix proteins [Niki *et al*, *Hepatology*, 29:858-67 (1999)], inflammatory diseases and cardiomyocyte hypertrophy [Lu *et al.*, PNAS, 97: 4070-4075 (2000)].

In another embodiment, the invention is also aimed at the treatment of protozoal infections including, but not limited to, malaria, toxoplasmosis and coccidiosis.

In another embodiment, the invention is aimed at the treatment of diseases caused by expanded polyglutamine repeats resulting in histone hypoacetylation including, but not limited to, neurodegenerative disorders such as Huntington's disease.

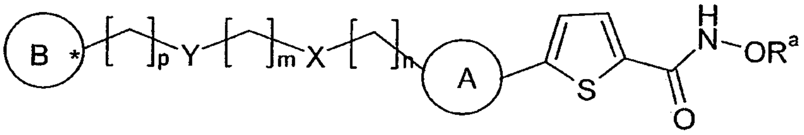
The compounds of formula (I) may be used or administered in combination with one or more additional drug(s) and/or procedures (such as radiotherapy in the case of cancer) useful in the treatment of the disorders mentioned above, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially. The additional drug(s) may or may not be HDAC inhbitors.

The thienyl-hydroxamic acids of the present invention may be prepared, for example, by the application or adaptation of methods described herein. They may also be prepared by known organic synthesis methods for example those described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

It may be necessary to protect reactive functional groups (e.g. hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of formula (I) to avoid their unwanted participation in a reaction leading to the formation of compounds of formula (I). Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons. 1999, may be used. In the reaction schemes provided below, all definitions of A, B, X Y, R^1 to R^5 are to be understood to include such protected functional groups.

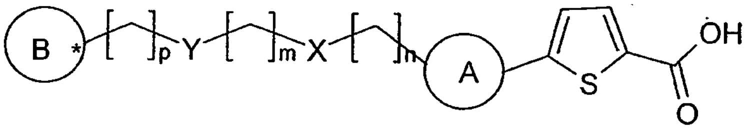
Preparation of compounds of formula (I)

One method for the preparation of compounds of formula (I) is the deprotection of compounds of formula (II), in which R^a is a suitable protecting group. Suitable protecting groups include benzyl, ^{t}butyloxycarbonyl, dimethyl^{t}butylsilyl, tetrahydropyranyl and Wang polystyrene resin. The reactions carried out depend on the nature of the protecting group, for example if the protecting group is benzyl, the reaction carried out is a hydrogenolysis in an inert solvent such as an alcohol like methanol or ethanol, in the presence of a noble metal catalyst such as palladium on a suitable carrier such as carbon or barium sulfate, at an appropriate temperature and pressure, such as ambient temperature and pressure. When the protecting group is tetrahydropyranyl or Wang polystyrene resin, the reaction is carried out in the presence of an acid, at a temperature between –20°C and 60°C, preferably between 0°C and ambient temperature. The acid may be a solution of hydrochloric acid in an inert solvent such as diethyl ether or dioxane, or trifluoroacetic acid in dichloromethane. Alternatively, when the protecting group is a silyl group, the reaction is carried out in the presence of a fluoride source such as tetrabutylammonium fluoride in an inert solvent such as dichloromethane.



(II)

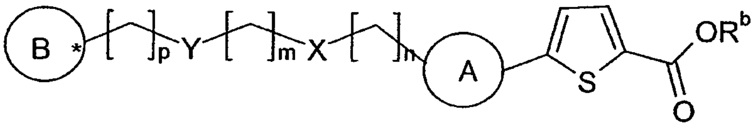
Compounds of formula (II) can be obtained from compounds of formula (III) by reaction with an appropriately protected hydroxylamine, such as *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, *O*-benzylhydroxylamine, *O*-Wang hydroxylamine polystyrene resin or *O*-(dimethyl^{t}butylsilyl)hydroxylamine. For example, reaction of compounds of formula (III) with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine is conveniently carried out using an activating agent such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and a base such as diisopropylethylamine in a suitable solvent such as *N,N*-dimethylformamide at an appropriate temperature such as ambient temperature.



(III)

An alternative method for the preparation of compounds of formula (I) involves the reaction of a compound of formula (III) with hydroxylamine. This reaction typically involves the use of an activating agent such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and a base such as diisopropylethylamine in a suitable solvent such as dimethylformamide at an appropriate temperature such as ambient temperature. Alternatively, a compound of formula (III) can be converted to a reactive derivative, such as an acid chloride or mixed anhydride. The reactive intermediate, is then treated with hydroxylamine in a suitable solvent, such as dichloromethane. The reactive intermediate may be used *in situ* without isolation, or it may be isolated and then treated with hydroxylamine.

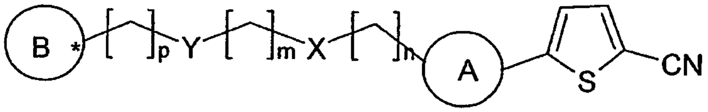
Another method for the preparation of compounds of formula (I) involves the reaction of a compound of formula (IV), in which R^b is a suitable protecting group, such as methyl or ethyl, with hydroxylamine. The reaction may be carried out in the presence of a base, such as potassium hydroxide, in a suitable solvent such as methanol. A co-solvent, such as *N,N*-dimethylacetamide may be used.



(IV)

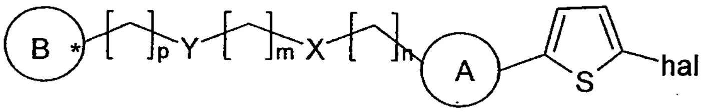
Compounds of formula (III) may be prepared by hydrolysis of compounds of formula (IV). The hydrolysis may be carried out using a suitable base such as sodium hydroxide, in a protic solvent such as ethanol, at an appropriate temperature, such as ambient temperature. Alternatively, the hydrolysis may be carried out under acidic conditions, for example using concentrated mineral acid, such as concentrated hydrochloric acid.

An alternative method for the preparation of compounds of (III) involves the hydrolysis of compounds of formula (V). The hydrolysis may be carried out using a suitable base, such as sodium hydroxide, in a protic solvent such as ethanol, at an appropriate temperature, such as the reflux temperature of the solvent.



(V)

An additional method for the preparation of compounds of formula (III) involves the use of a compound of formula (VI), in which "hal" means chloro, bromo or iodo. A compound of formula (VI) can be converted into a compound of formula (III) by any suitable method known to those skilled in the art, including the use of a palladium catalysed carbonylation reaction, or a halogen/lithium exchange followed by quenching with carbon dioxide. The carbonylation reaction can be carried out using carbon monoxide in the presence of a suitable catalyst, such as bis(triphenylphosphine) palladium chloride and a suitable base, such as triethylamine in appropriate solvent(s), such as methanol and water. The reaction may be carried out at any appropriate temperature and pressure, such as a temperature of 110^{O}C and a pressure of 10 bar. The halogen/lithium exchange reaction may be carried out in the presence of a suitable lithium base, such as ^{n}butyl lithium, in an appropriate solvent such as tetrahydrofuran, at an appropriate temperature such as 0°C.

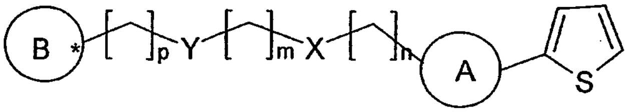


(VI)

Compounds of formula (VI) may also be used to prepare compounds of fomula (IV) if the carbonylation reaction is carried out in the presence of an alcohol, such as methanol or ethanol. Alternatively, subjection of a compound of formula (VI) to halogen/lithium exchange followed by quenching with a suitable chloroformate, such as ethyl chloroformate, will also provide a compound of formula (IV).

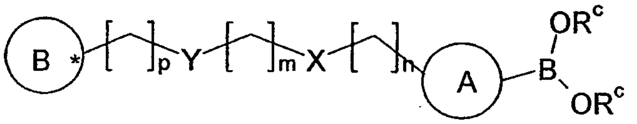
Compounds of formula (V) may be prepared from compounds of formula (VI) by reaction with zinc cyanide in the presence of a palladium (0) catalyst, for example tetrakis (triphenylphospine)palladium (0), in an inert solvent, for example *N*,*N*-dimethylformamide, at temperatures from about room temperature up to reflux temperature.

Compounds of formula (VI) may be prepared from compounds of formula (VII) by reaction with an appropriate halogenating agent, such as bromine, iodine, *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-iodosuccinimide, in an appropriate solvent, such as dichloromethane.

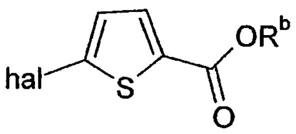


(VII)

Compounds of formula (IV) may be prepared from compounds of formula (VIII), in which R^c represents hydrogen, lower alkyl, or $-B(OR^c)_2$ represents a cyclic boronate ester, and a compound of formula (IX), in which "hal" and R^b are as previously defined. The reaction may be performed in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), and a suitable base, such as cesium carbonate, in an appropriate solvent such as *N,N*-dimethylformamide, at a suitable temperature, such as an elevated temperature, such as 80°C.

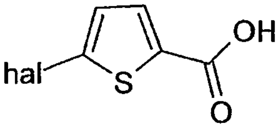


(VIII)

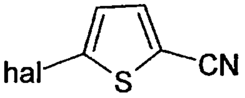


(IX)

In a similar manner, compounds of formula (III) may be prepared from compounds of formula (VIII) and a compound of formula (X), and compounds of formula (V) can be prepared starting from compounds of formula (XI).

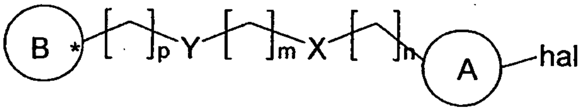


(X)

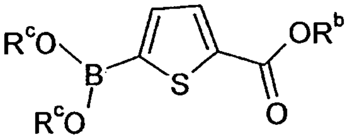


(XI)

An alternative method for the preparation of compounds of formula (IV) involves the reaction of a compound of formula (XII), in which hal is as previously defined, with a compound of formula (XIII) in which R^b and R^c are as previously defined. The reaction may be performed in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), and a suitable base, such as cesium carbonate, in an appropriate solvent such as *N,N*-dimethylformamide, at a suitable temperature, such as an elevated temperature, such as 80°C.

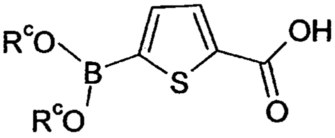


(XII)

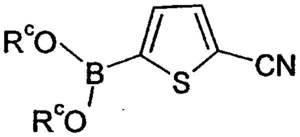


(XIII)

In a similar manner, compounds of formula (III) may be prepared from compounds of formula (XII) and a compound of formula (XIV), and compounds of formula (V) can be prepared starting from compounds of formula (XV).



(XIV)



(XV)

Further methods for forming a chemical bond between A and the thienyl ring system to synthesise compounds of formula (II), (III), (IV), (V), (VI) and (VII) will be evident to one skilled in the art. These methods include replacement of any combination of the following: boronic acid or boronate ester (e.g. with a trialkyl tin, or a zinc halide such as zinc iodide, bromide or chloride); halogen (e.g. with a triflate); solvent; catalyst; temperature; or base. A list of examples of alternative biaryl bond forming reactions which could be used are described by Fu *et al.* *J. Am. Chem. Soc.*, 123: 2719-2724 (2001) and Lemaire *et al.* *Chem. Rev.*, 102: 1359-1469 (2002), and references therein. It may also be possible to carry out a biaryl bond forming reaction using an appropriately substituted thiophene hydroxamic acid, or protected hydroxamic acid.

Compounds of formula (XIII), (XIV) and (XV) may be commercially available, or may be prepared from compounds of formula (IX), (X) or (XI) respectively by conversion to a suitable organometallic reagent, such as a lithium or magnesium reagent and subsequent treatment with a suitable boron reagent, such as trimethylborate. Alternatively, compounds of formula (IX), (X) or (XI) may be treated with a suitable boron reagent, such as bis(pinacolato)diboron, in the presence of a suitable catalyst, such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium, and a suitable base, such as potassium acetate, in an appropriate solvent, such as dioxane, at a suitable temperature, for example room temperature to the reflux temperature of the solvent.

Compounds of formula (IX), (X) and (XI) may be either commercially available, or may be prepared using any suitable method known to those skilled in the art.

Compounds of formula (VIII) may be prepared from compounds of formula (XII) using the procedures described above for the conversion of compounds of formula (IX), (X) or (XI) into compounds of formula (XIII), (XIV) and (XV).

Compounds of formula (XII) may be prepared using any suitable procedure known to those skilled in the art, including standard functional group interconversions.

For example primary amine (-NH_2) groups may be alkylated using a reductive alkylation process employing an aldehyde or a ketone and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example 1,2-dichloroethane, or an alcohol such as ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Secondary amine (-NH-) groups may be similarly alkylated employing an aldehyde.

In a further example, primary amine or secondary amine groups may be converted into amide groups (-NHCOR' or -NRCOR') by acylation. Acylation may be achieved by reaction with an appropriate acid chloride in the presence of a base, such as triethylamine, in a suitable solvent, such as dichloromethane, or by reaction with an appropriate carboxylic acid in the presence of a suitable coupling agent such HATU (*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate) in a suitable solvent such as dichloromethane. Similarly, amine groups may be converted into sulphonamide groups (-$NHSO_2R'$ or -$NR''SO_2R'$) groups by reaction with an appropriate sulphonyl chloride in the presence of a suitable base, such as triethylamine, in a suitable solvent such as dichloromethane. Primary or secondary amine groups can be converted into urea groups (-NHCONR'R" or -NRCONR'R") by reaction with an appropriate isocyanate in the presence of a suitable base such as triethylamine, in a suitable solvent, such as dichloromethane.

An amine (-NH_2) may be obtained by reduction of a nitro (-NO_2) group, for example by catalytic hydrogenation, using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethyl acetate or an alcohol e.g. methanol. Alternatively, the transformation may be carried out by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example, amine (-CH_2NH_2) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from –78°C to the reflux temperature of the solvent.

In a further example, amine (-NH_2) groups may be obtained from carboxylic acid groups (-CO_2H) by conversion to the corresponding acyl azide (-CON_3), Curtius rearrangement and hydrolysis of the resultant isocyanate (-N=C=O).

Aldehyde groups (-CHO) may be converted to amine groups (-$CH_2NR'R''$)) by reductive amination employing an amine and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example dichloromethane, or an alcohol such as ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, aldehyde groups may be converted into alkenyl groups (-CH=CHR') by the use of a Wittig or Wadsworth-Emmons reaction using an appropriate phosphorane or phosphonate under standard conditions known to those skilled in the art.

Aldehyde groups may be obtained by reduction of ester groups (such as -CO_2Et) or nitriles (-CN) using diisobutylaluminium hydride in a suitable solvent such as toluene. Alternatively, aldehyde groups may be obtained by the oxidation of alcohol groups using any suitable oxidising agent known to those skilled in the art.

Ester groups (-CO_2R') may be converted into the corresponding acid group (-CO_2H) by acid- or base-catalused hydrolysis, depending on the nature of R. If R is t-butyl, acid-catalysed hydrolysis can be achieved for example by treatment with an organic acid such as trifluoroacetic acid in an aqueous solvent, or by treatment with an inorganic acid such as hydrochloric acid in an aqueous solvent.

Carboxylic acid groups (-CO_2H) may be converted into amides (-CONHR' or -CONR'R") by reaction with an appropriate amine in the presence of a suitable coupling agent, such as HATU, in a suitable solvent such as dichloromethane.

In a further example, carboxylic acids may be homologated by one carbon (i.e -CO_2H to -CH_2CO_2H) by conversion to the corresponding acid chloride (-COCl) followed by Arndt-Eistert synthesis.

In a further example, -OH groups may be generated from the corresponding ester (e.g. -CO_2R'), or aldehyde (-CHO) by reduction, using for example a complex metal hydride such as lithium aluminium hydride in diethyl ether or tetrahydrofuran, or sodium borohydride in a solvent such as methanol. Alternatively, an alcohol may be prepared by reduction of the corresponding acid (-CO_2H), using for example lithium aluminium hydride in a solvent such as tetrahydrofuran, or by using borane in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. *p*-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon (e.g. dichloromethane) to yield the corresponding chloride. A base (e.g. triethylamine) may also be used in the reaction.

In another example, alcohol or phenol groups may be converted to ether groups by coupling an alcohol or phenol with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl, or dimethylazodicarboxylate. Alternatively ether groups may be prepared by deprotonation of an alcohol or phenol, using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkyl halide.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as ^{n}butyl or ^{t}butyl lithium, optionally at a low temperature, e.g. around –78°C, in a solvent such as tetrahydrofuran, and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using *N,N*-dimethylformamide as the electrophile. Aromatic halogen substituents may alternatively be subjected to metal (e.g. palladium or copper) catalysed reactions, to introduce, for example, acid, ester, cyano, amide, aryl, heterary1, alkenyl, alkynyl, thio- or amino substituents. Suitable procedures which may be employed include those described by Heck, Suzuki, Stille, Buchwald or Hartwig.

Aromatic halogen substituents may also undergo nucleophilic displacement following reaction with an appropriate nucleophile such as an amine or an alcohol. Advantageously, such a reaction may be carried out at elevated temperature in the presence of microwave irradiation.

In another example aromatic halogen substituents may also undergo vinylation reactions with a reagent such as tributylvinyl tin, in a suitable solvent such as toluene, at an appropriate temperature such as 80^{O}C.

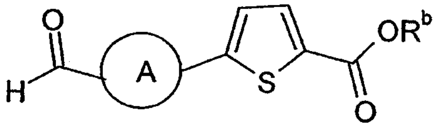
As another example, compounds of formula (I) in which R^1 is heteroaryl containing an *N*-oxide group (e.g. pyridine-*N*-oxide) may be prepared by oxidation of compounds of formula (I) in which R^1 is the corresponding non-oxidised heteroaryl.

Alkenes may be oxidised to provide *cis*-diols using osmium tetraoxide in a suitable solvent, such as aqueous tetrahydrofuran.

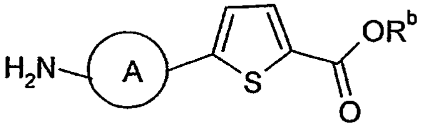
Cis-diols may be oxidised to aldehydes and/or ketones using a suitable reagent such as sodium *meta*-periodate in a suitable solvent such as aqueous tetrahydrofuran.

Alkenes can also be converted to aldehydes and/or ketones by ozonolysis using a suitable solvent such as dichloromethane, at a suitable temperature such as –78^{O}C, followed by the addition of a suitable reducing agent, such as dimethyl sulfide.

It will be appreciated by those skilled in the art that the functional group interconversions described above may be carried out at any suitable stage of the synthesis. Thus, for example, compounds of formula (IV) may be prepared from compounds of formula (XVI) or formula (XVII) using standard functional group interconversions such as those described above.

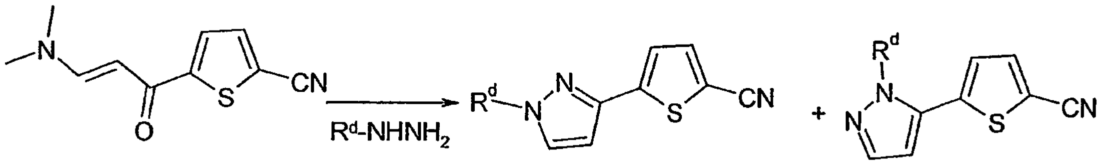


(XVI)



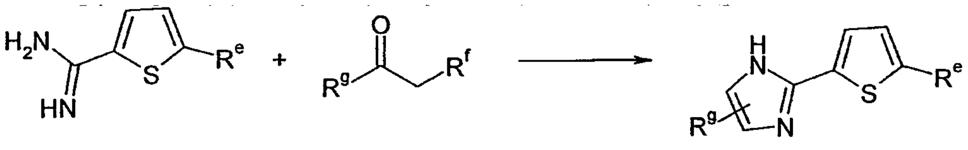
(XVII)

Compounds of formula (V) in which A represents a 3-pyrazolyl may be prepared from the compound of formula (XVIII) by treatment with a hydrazine of formula (XIX), in which R^d represents H, B-$(CH_2)_p$-Y-$(CH_2)_m$-X-$(CH_2)_n$-, or a group convertible to B-$(CH_2)_p$-Y-$(CH_2)_m$-X-$(CH_2)_n$-, in a suitable solvent, such as a protic solvent, for example ethanol, at an appropriate temperature. It will be recognised that such reactions may give rise to two regioisomers, which may be separated using any standard techniques known to those skilled in the art, such as chromatography. The compound of formula (XVIII) is commercially available. Alternatively, if the reaction is carried out using hydrazine itself (i.e R^d represents H), the product may be further elaborated by alkylation of the ring nitrogen atom.



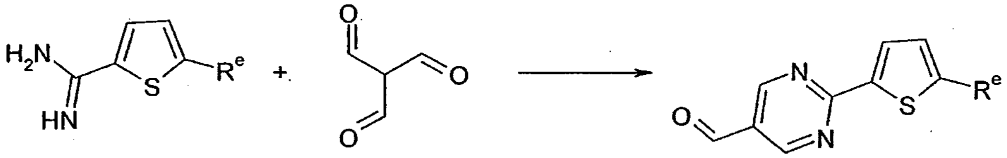
(XVIII) (XIX)

Compounds of formula (VI) or (VII) in which A represents a 2-imidazolyl and R^e represents hydrogen or halogen (such as iodide, bromide or chloride) may be prepared from the compound of formula (XX) by treatment with a compound of formula (XXI), in which R^f represents a hydroxyl, halogen (such as chloride, bromide or iodide), or alternative leaving group, and R^g represents a variety of carbon linked substituents, with a suitable base and solvent, such as aqueous hydroxylamine, at an appropriate temperature. Compounds of formula (XXII) may be converted into compounds of formula (VI) or (VII) using standard functional group interconversions described herewithin.



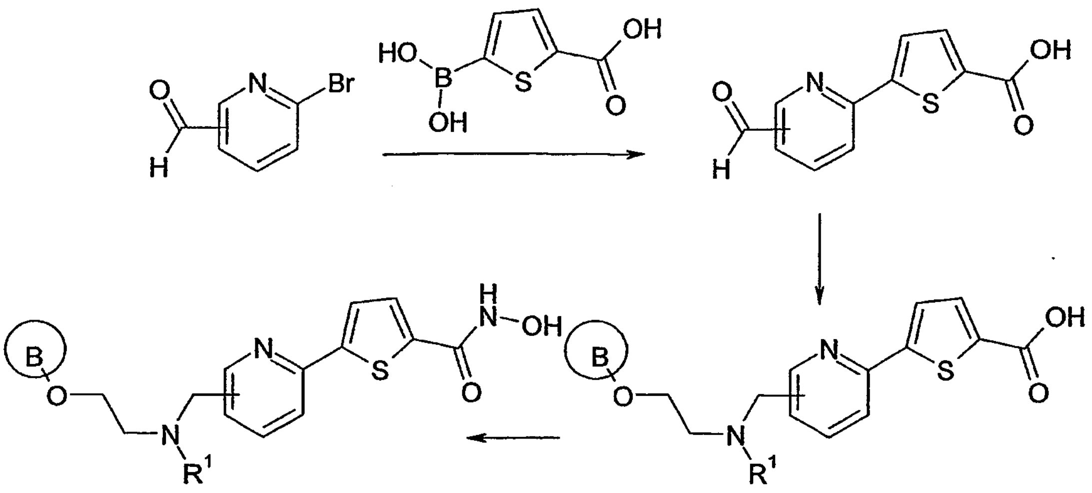
(XX) (XXI) (XXII)

Compounds of formula (VI) or (VII) in which A represents a 2-pyrimidinyl and R^e represents hydrogen or halogen (such as iodide, bromide or chloride) may be prepared from the compound of formula (XX) by treatment with a compound of formula (XXIII), in a suitable solvent, such as ethanol, at an appropriate temperature such as reflux temperature. Compounds of formula (XXIV) may be converted into compounds of formula (VI) or (VII) using standard functional group interconversions described herewithin.

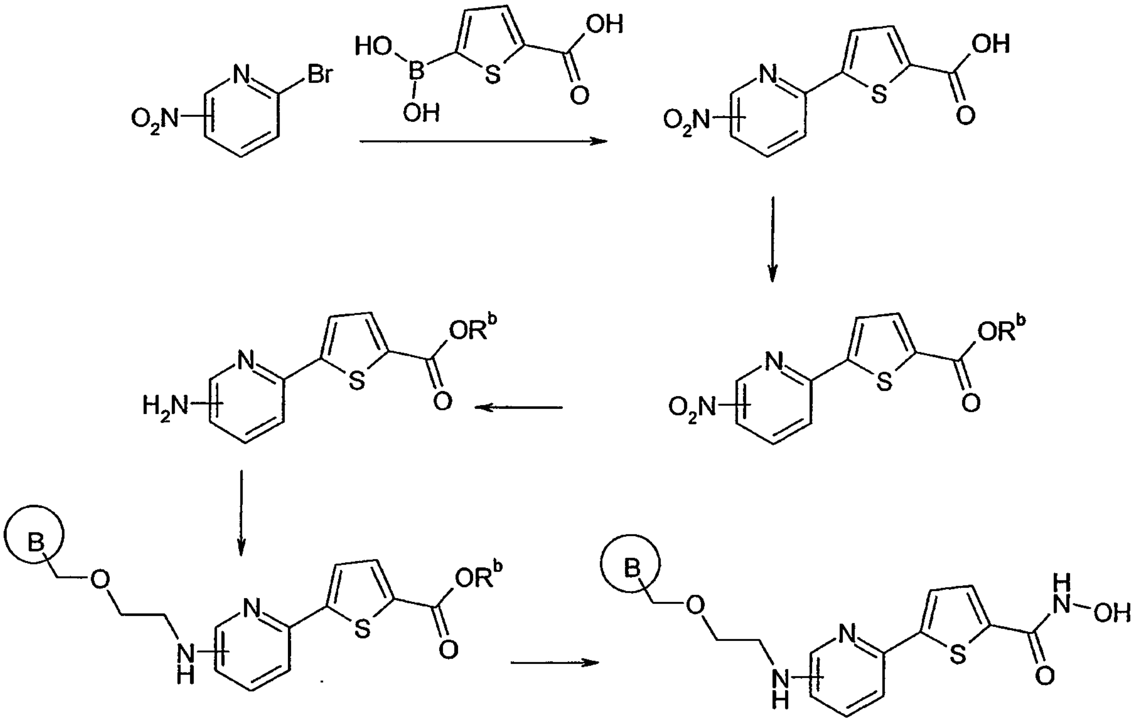


(XX) (XXIII) (XXIV)

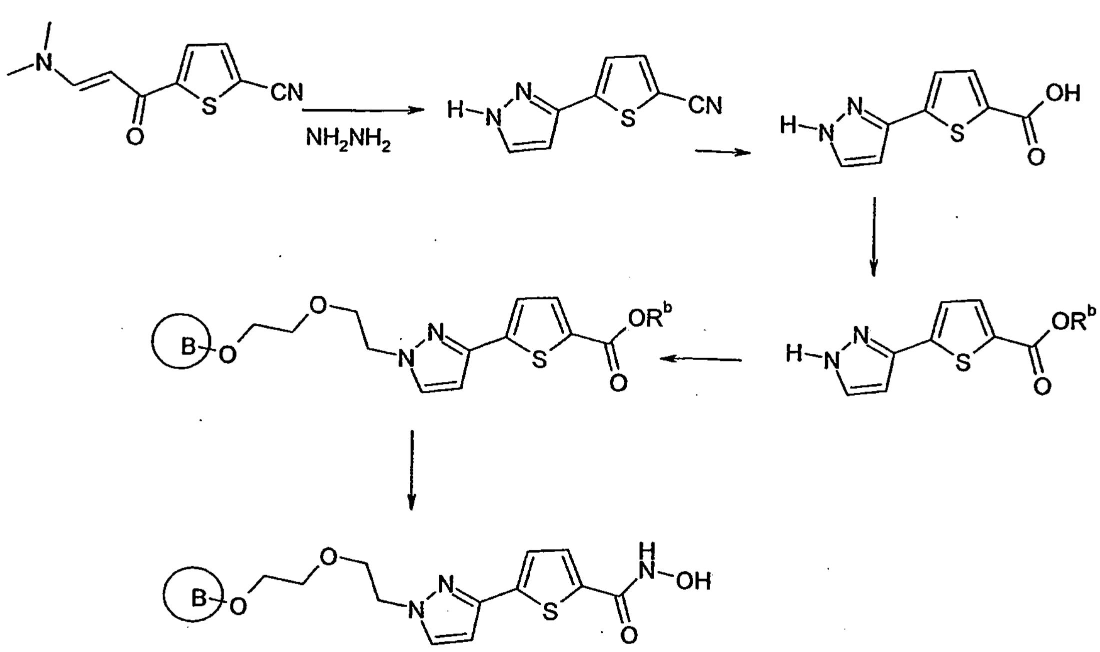
For the purpose of illustration, some typical synthetic sequences are provided in Schemes 1, 2, 3 4 and 5.



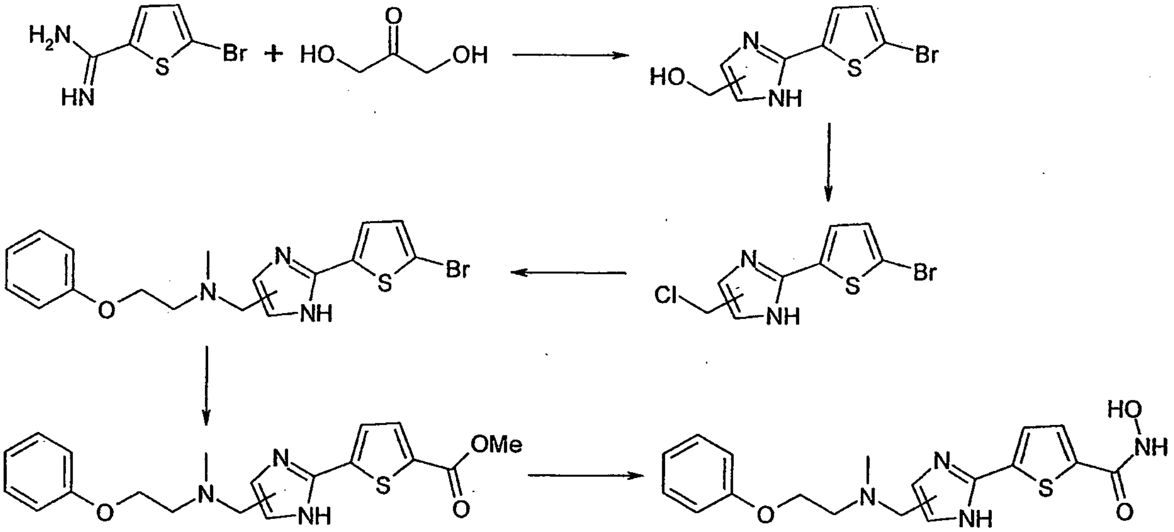
Scheme 1



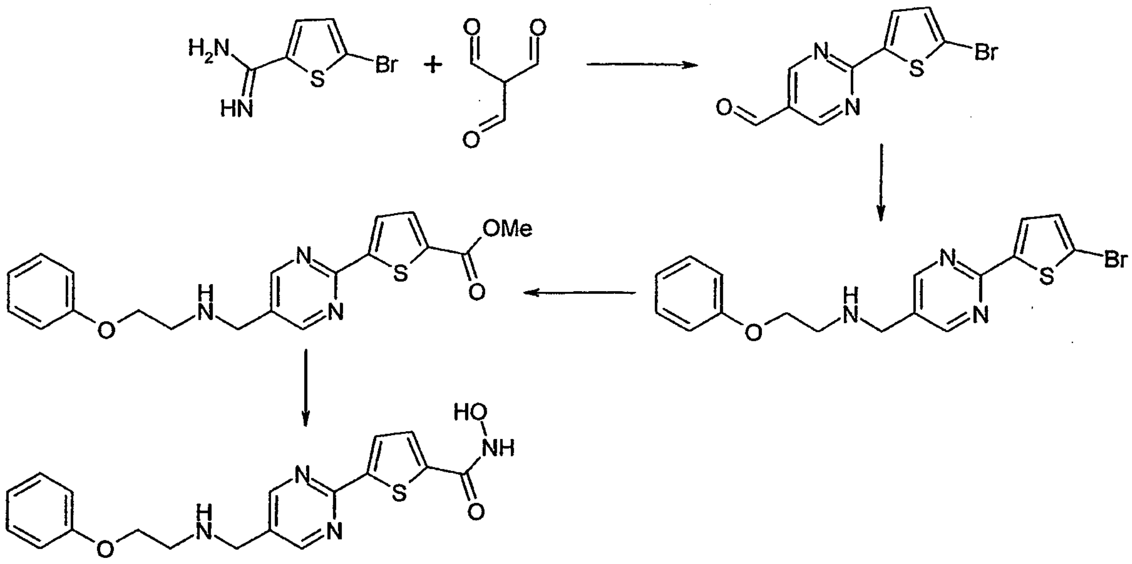
Scheme 2



Scheme 3



Scheme 4



Scheme 5

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.* intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form (*e.g.* in ampoules or in multi-dose containers, with an added preservative). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilising and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, (*e.g.* sterile pyrogen-free water), before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, (*e.g.* containing conventional suppository bases such as cocoa butter or other glycerides).

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, (*e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

400MHz ^1H nuclear magnetic resonance spectra (NMR) were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5mm probe. In the NMR, chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, dt = double triplet, t = triplet, td = triple doublet, q = quartet.

High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times (R_T) and associated mass ions were performed using one of the following methods.

Method A: Experiments performed on a Finnigan TSQ700 spectrometer with positive ion electrospray and single wavelength UV 254nm detection using a Higgins Clipeus C18 5μm 100 x 3.0mm column and a 2 ml / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 2 minutes.

Method B: Experiments performed on a Micromass Platform LC spectrometer with positive and negative ion electrospray and ELS/Diode array detection using a Phenomenex Luna C18(2) 30 x 4.6mm column and a 2 ml / minute flow rate. The solvent system was 95% solvent A and 5% solvent B for the first 0.50 minutes followed by a gradient up to 5%

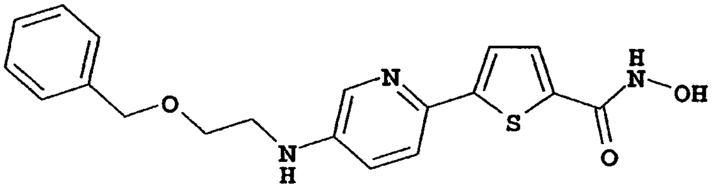
solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 0.50 minutes.

Reverse-phase High Pressure Liquid Chromatography (HPLC) purification was performed using a Genesis HPLC Column (Ref. 16R10985, 100mmx22.5mm) containing C18-7μm 120A silica.

Compounds have been named using Beilstein Autonom software.

Example 1:

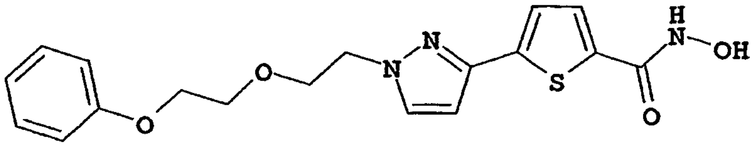
5-[5-(2-Benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide



To a solution of 5-[5-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid methyl ester (69mg, 0.18mmol, Intermediate 1) in methanol (4ml), was added hydroxylamine hydrochloride (130mg, 1.87mmol) followed by potassium hydroxide powder (167mg, 3.0mmol). After stirring overnight the reaction mixture was diluted with 10% citric acid solution and extracted twice with ethyl acetate. The organic phases were combined and washed with saturated sodium hydrogen carbonate solution, followed by brine, dried (Na_2SO_4), then evaporated to give a residue. The residue was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 5:95 to 95:5, v/v, over 90 minutes) as eluent, to provide 5-[5-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide (19mg) as a yellow solid. ^{1}H NMR (CD_3OD): δ 7.94 (d br, 1H), 7.70 (d, 1H), 7.56 (apparent s, 1H), 7.46 (d, 1H), 7.22-7.35 (m, 6H), 4.56 (s, 2H), 3.70 (t, 2H), 3.42 (t, 2H). LCMS (Method A): R_T = 5.78 minutes; 370 $(M+H)^+$.

Example 2: (similarly prepared to Example 1, but using Intermediate 5)

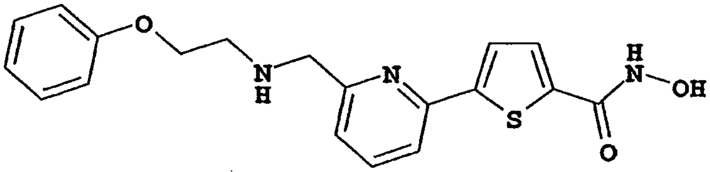
5-{1-[2-(2-Phenoxy-ethoxy)-ethyl]-1*H*-pyrazol-3-yl}-thiophene-2-carboxylic acid hydroxyamide



LCMS (Method A): $R_T = 7.03$ minutes; 374 $(M+H)^+$.

Example 3:

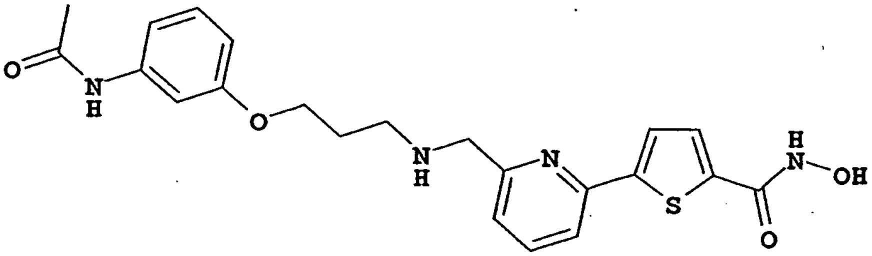
5-{6-[(2-Phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (103mg, 0.23mmol, Intermediate 9) in dichloromethane (4.5ml) was treated with trifluoroacetic acid (0.5ml) and a drop of water. The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue. The residue was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 20:80 to 95:5, v/v, over 90 minutes) as eluent, to provide 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide (3.8mg) as a light-brown oil. ^{1}H NMR (CD_3OD): δ 7.92 (m, 2H), 7.77 (d, 1H), 7.58 (apparent s, 1H), 7.39 (m, 1H), 7.32 (m, 2H), 7.05 (m, 2H), 7.00 (m, 2H), 4.54 (s, 2H), 4.39 (t, 2H), 3.66 (t, 2H). LCMS (Method A): $R_T = 3.62$ minutes; 370 $(M+H)^+$.

Example 4:

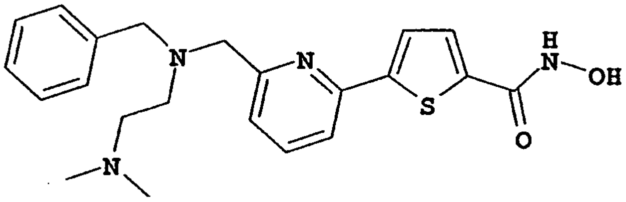
5-(6-{[3-(3-Acetylamino-phenoxy)-propylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



To a slowly stirred suspension of 5-(6-{[3-(4-acetylamino-phenoxy)-propylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (70mg, 0.16mmol, Intermediate 12), hydroxylamine Wang® resin (200mg, 1.0 mmol/g loading) and pyridine (40μl, 0.5mmol) in dimethylformamide (3ml) was added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (71mg, 0.18mmol). The mixture was stirred at room temperature overnight, then filtered. The resin was washed alternatively with methanol and dichloromethane (3x) and dried. The resin was treated with 20% trifluoroacetic acid in dichloromethane solution (5ml), stirred gently for 30 minutes, filtered, and washed with dichloromethane. The filtrate was concentrated to give a brown oil, which was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 5:95 to 5:95, v/v, over 90 minutes) as eluent, to provide 5-(6-{[3-(3-acetylamino-phenoxy)-propylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (3.2mg) as a colourless oil. LCMS (Method B): $R_T = 1.79$ minutes; 441 $(M+H)^+$.

Example 5: (similarly prepared to Example 4, but using Intermediate 13)

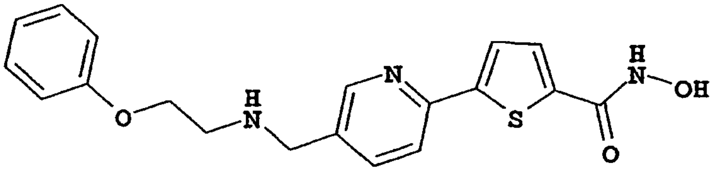
5-(6-{[Benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



LCMS (Method B): $R_T = 2.06$ minutes; 411 $(M+H)^+$.

Example 6: (similarly prepared to Example 3, but using Intermediate 14)

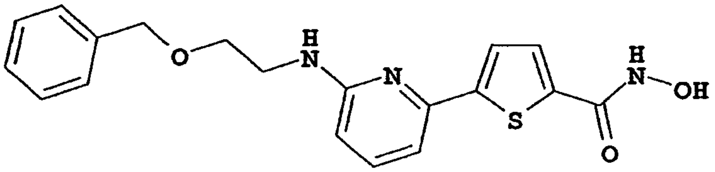
5-{5-[(2-Phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD$_3$OD): δ 8.66 (s, 1H), 7.97 (m, 2H), 7.74 (d, 1H), 7.59 (apparent s, 1H), 7.30 (m, 2H), 6.99 (m, 3H), 4.34 (s, 2H), 4.29 (t, 2H), 3.49 (t, 2H). LCMS (Method A): R$_T$ = 4.05 minutes; 370 (M+H)$^+$.

Example 7:

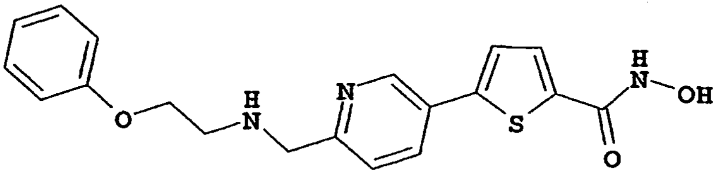
5-[6-(2-Benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-[6-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (361mg, 0.8mmol, Intermediate 17) in methanol (2ml) was treated with *p*-toluene sulfonic acid (7mg, 0.03mmol). The solution was stirred at room temperature for 1 hour, then concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The two phases were separated and the organic phase was washed with water, then dried over sodium sulfate and then evaporated under reduced pressure to provide 5-[6-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide (140mg) as a solid. ^{1}H NMR (CD$_3$OD): δ 7.68 (apparent t br, 1H), 7.51 (m br, 2H), 7.20-7.30 (m, 5H), 7.10 (d, 1H), 6.77 (d br, 1H), 4.59 (s, 2H), 3.78 (t, 2H), 3.68 (2H). LCMS (Method A): R$_T$ = 6.25 minutes; 370 (M+H)$^+$.

Example 8:

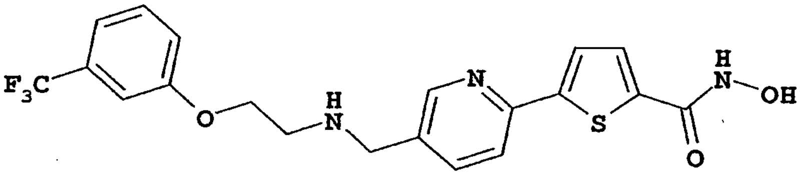
5-{6-[(2-Phenoxy-ethylamino)-methyl]-pyridin-3-yl}-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-3-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (196mg, 0.35mmol, Intermediate 20) in dichloromethane (8ml) was treated with trifluoroacetic acid (2ml). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue, which was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 15:85 to 45:55, v/v, over 20 minutes) as eluent. The combined fractions were collected, concentrated and triturated with diethyl ether, to provide 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-3-yl}-thiophene-2-carboxylic acid hydroxyamide (125mg) as a white powder. ^{1}H NMR (CD_3OD): δ 8.95 (d, 1H), 8.15 (dd, 1H), 7.60 (apparent s, 1H), 7.54 (d, 1H), 7.53 (d, 1H), 7.31 (m, 2H), 7.01 (m, 3H), 4.51 (s, 2H), 4.34 (t, 2H), 3.58 (t, 2H). LCMS (Method A): R_T = 3.85 minutes; 370 $(M+H)^+$.

Example 9:

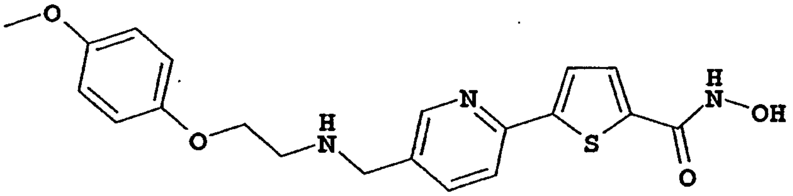
5-(5-{[2-(3-Trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of {6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-[2-(3-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester (134mg, 0.22mmol, Intermediate 24) in dichloromethane (5ml) and methanol (40μl) was treated with trifluoroacetic acid (1ml) and water (20μl). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue. The residue was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 5:95 to 55:45, v/v, over 40 minutes) as eluent, to provide 5-(5-{[2-(3-trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (25mg) as an off-white solid. ^{1}H NMR (CD_3OD): δ 8.67 (apparent s, 1H), 7.99 (dd, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.59 (apparent s, 1H), 7.52 (t, 1H), 7.29 (m, 3H), 4.38 (s, 2H), 4.37 (t, 2H), 3.56 (t, 2H). LCMS (Method A): R_T = 4.95 minutes; 438 $(M+H)^+$.

Example 10: (similarly prepared to Example 9, but using Intermediate 26)

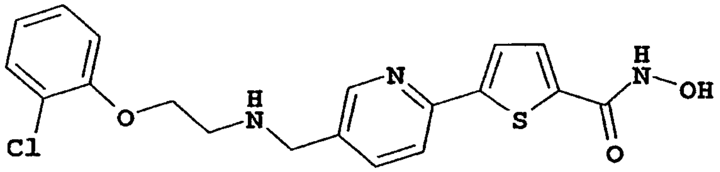
5-(5-{[2-(4-Methoxy-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD_3OD): δ 8.66 (apparent s, 1H), 7.97 (m, 2H), 7.73 (d, 1H), 7.59 (apparent s, 1H), 6.93 (m, 2H), 6.86 (m, 2H), 4.35 (s, 2H), 4.23 (t, 2H), 3.73 (s, 3H), 3.47 (t, 2H). LCMS (Method A): R_T = 3.97 minutes; 400 $(M+H)^+$.

Example 11: (similarly prepared to Example 9, but using Intermediate 28)

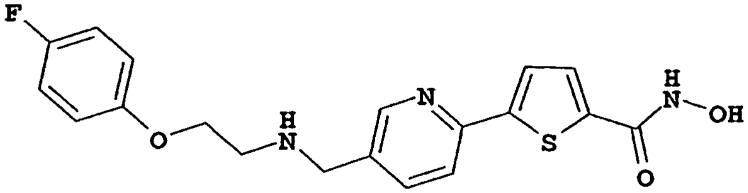
5-(5-{[2-(2-Chloro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD_3OD): δ 8.68 (apparent s, 1H), 8.00 (dd, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.59 (apparent s, 1H), 7.42 (dd, 1H), 7.31 (m, 1H), 7.15 (dd, 1H), 7.02 (td, 1H), 4.45 (s, 2H), 4.39 (t, 2H), 3.57 (t, 2H). LCMS (Method A): R_T = 4.56 minutes; 404 & 406 $(M+H)^+$.

Example 12:

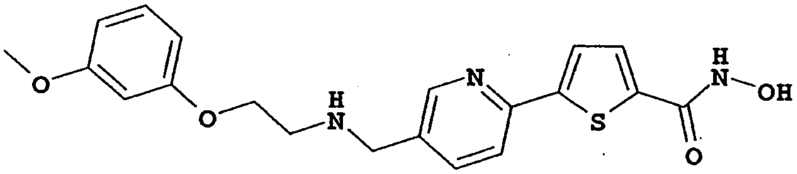
5-(5-{[2-(4-Fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of [2-(4-fluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester (61mg, 0.11mmol, Intermediate 30) in dichloromethane (3ml) and methanol (20μl) was treated with 4N hydrochloric acid in dioxan (0.3ml). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue, which was triturated with diethyl ether to provide an off-white solid. The off-white solid was recrystallised using methanol and concentrated hydrochloric acid, to provide 5-(5-{[2-(4-fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (11mg) as a yellow solid. ^{1}H NMR (CD$_3$OD): δ 8.68 (dd, 1H), 8.01 (dd, 1H), 7.98 (dd, 1H), 7.75 (d, 1H), 7.60 (apparent s, 1H), 7.05 (m, 2H), 7.01 (m, 2H), 4.40 (s, 2H), 4.29 (t, 2H), 3.55 (t, 2H). LCMS (Method A): R$_T$ = 4.02 minutes; 388 (M+H)$^+$.

Example 13: (similarly prepared to Example 12, but using Intermediate 34)

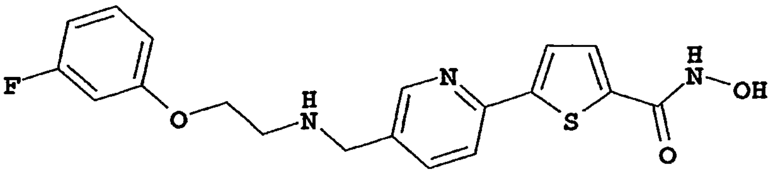
5-(5-{[2-(3-Methoxy-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD$_3$OD): δ 8.71 (d, 1H), 8.09 (dd, 1H), 8.02 (d, 1H), 7.78 (d, 1H), 7.61 (apparent s, 1H), 7.20 (m, 1H), 6.55-6.61 (m, 3H), 4.42 (s, 2H), 4.30 (t, 2H), 3.77 (s, 3H), 3.55 (t, 2H). LCMS (Method A): R$_T$ = 4.04 minutes; 400 (M+H)$^+$.

Example 14:

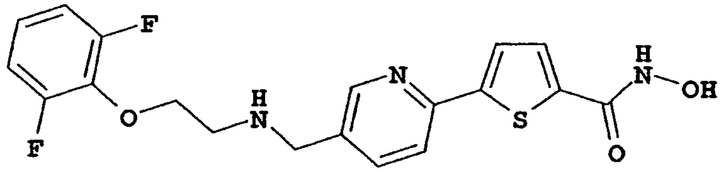
5-(5-{[2-(3-Fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of [2-(3-fluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester (31mg, 0.054mmol, Intermediate 37) in dichloromethane (3ml) and methanol (20µl) was treated with 4N hydrochloric acid in dioxan (0.3ml). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue. The residue was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 5:95 to 45:55, v/v, over 40 minutes) as eluent, to provide 5-(5-{[2-(3-fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (9mg). ^{1}H NMR (CD_3OD): δ 8.67 (s, 1H), 7.99 (d, 1H), 7.97 (d, 1H), 7.74 (d, 1H), 7.59 (apparent s, 1H), 7.31 (td, 1H), 6.83 (dd, 1H), 6.79 (dt, 1H), 6.74 (td, 1H), 4.37 (s, 1H), 4.31 (t, 1H), 3.53 (t, 1H). LCMS (Method A): R_T = 4.01 minutes; 388 $(M+H)^+$.

Example 15:

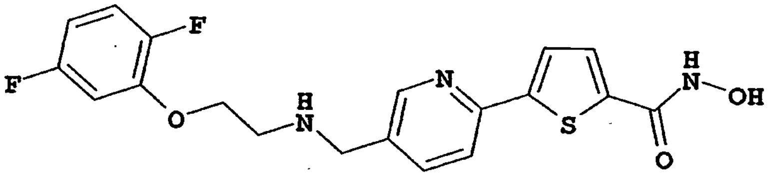
5-(5-{[2-(2,6-Difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of [2-(2,6-difluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester (51mg, 0.086mmol, Intermediate 40) in dichloromethane (3ml) and methanol (20µl) was treated with 4N hydrochloric acid in dioxan (0.3ml). The solution was stirred for 3 hours, and then concentrated under reduced pressure to give a residue. The residue was triturated with diethyl ether and then acetonitrile, to provide 5-(5-{[2-(2,6-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (29mg). ^{1}H NMR (CD_3OD): δ 8.69 (s, 1H), 8.03 (d, 1H), 7.99 (d, 1H), 7.75 (d, 1H), 7.60 (apparent s, 1H), 7.16 (m, 1H), 7.06 (m, 2H), 4.44 (m, 4H), 3.56 (t, 2H). LCMS (Method A): R_T = 4.03 minutes; 406 $(M+H)^+$.

Example 16: (similarly prepared to Example 15, but using Intermediate 43)

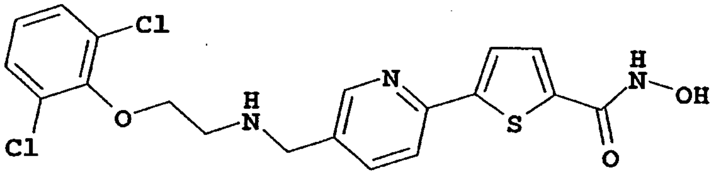
5-(5-{[2-(2,5-Difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^1H NMR (CD_3OD): δ 8.68 (d, 1H), 8.02 (dd, 1H), 7.98 (d, 1H), 7.75 (d, 1H), 7.59 (apparent s, 1H), 7.17 (ddd, 1H), 7.02 (m, 1H), 6.75 (ddt, 1H), 4.42 (s, 2H), 4.41 (t, 2H), 3.60 (t, 2H). LCMS (Method A): R_T = 4.11 minutes; 406 $(M+H)^+$.

Example 17: (similarly prepared to Example 15, but using Intermediate 46)

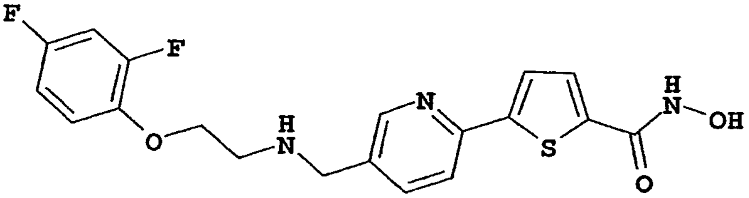
5-(5-{[2-(2,6-Dichloro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^1H NMR (CD_3OD): δ 8.71 (d, 1H), 8.04 (dd, 1H), 8.00 (d, 1H), 7.76 (d, 1H), 7.60 (apparent s, 1H), 7.45 (d, 2H), 7.18 (t, 1H), 4.47 (s, 2H), 4.36 (t, 2H), 3.62 (t, 2H). LCMS (Method A): R_T = 4.63 minutes; 438 $(M+H)^+$.

Example 18:

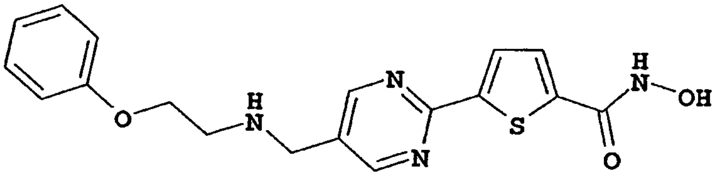
5-(5-{[2-(2,4-Difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of [2-(2,4-difluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester (51mg, 0.086mmol, Intermediate 49) in dichloromethane (3ml) and methanol (20μl) was treated with 4N hydrochloric acid in dioxan (0.3ml). The solution was stirred for 3.5 hours, and then concentrated under reduced pressure to give a residue. The residue was triturated with diethyl ether, and then recrystallised from methanol, to provide 5-(5-{[2-(2,4-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (32mg). ^{1}H NMR (CD$_3$OD): δ 8.68 (apparent s, 1H), 8.01 (dd, 1H), 7.98 (d, 1H), 7.74 (d, 1H), 7.59 (apparent s, 1H), 7.19 (td, 1H), 7.05 (m, 1H), 6.92 (m, 1H), 4.41 (s, 2H), 4.37 (t, 2H), 3.56 (t, 2H). LCMS (Method A): R_T = 4.12 minutes; 406 $(M+H)^+$.

Example 19: (similarly prepared to Example 8, but using Intermediate 52)

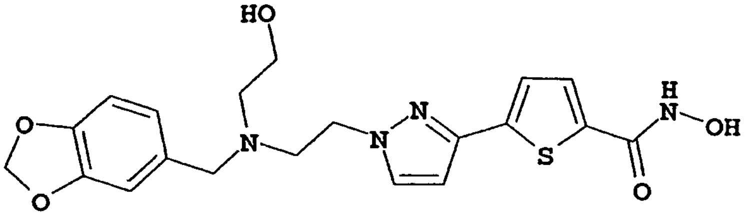
5-{5-[(2-Phenoxy-ethylamino)-methyl]-pyrimidin-2-yl}-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR [(CD$_3$)$_2$SO]: δ 11.42 (s, 1H), 9.27 (s, 1H), 9.14 (s br, 2H), 8.94 (s, 2H), 7.96 (d, 1H), 7.66 (d br, 1H), 7.33 (m, 2H), 7.00 (m, 3H), 4.33 (s, 2H), 4.25 (t, 2H), 3.44 (t, 2H). LCMS (Method A): R_T = 4.82 minutes; 371 $(M+H)^+$.

Example 20:

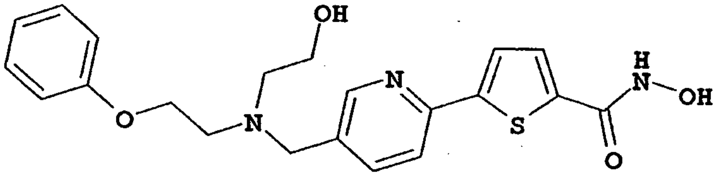
5-(1-{2-[Benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (169mg, 0.33mmol, Intermediate 58) in dichloromethane (10ml) and methanol (40µl) was treated with 4N hydrochloric acid in dioxan (0.5ml). The solution was stirred for 2 hours, and then concentrated under reduced pressure to give a residue. The residue was triturated with acetonitrile and diethyl ether, followed by acetonitrile, to provide 5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid hydroxyamide – hydrochloride salt (59mg) as a white solid. ^{1}H NMR [$(CD_3)_2SO$]: δ 11.23 (s, 1H), 10.13 (s, 1H), 7.91 (d, 1H), 7.57 (apparent s, 1H), 7.40 (d, 1H), 7.20 (d, 1H), 7.07 (dd, 1H), 6.98 (d, 1H), 6.07 (s, 2H), 4.68 (t, 2H), 4.36 (m br, 2H), 3.76 (m br, 2H), 3.61 (m br, 2H), 3.19 (t br, 2H). LCMS (Method A): R_T = 3.53 minutes; 431 $(M+H)^+$.

Example 21:

5-(5-{[(2-Hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide

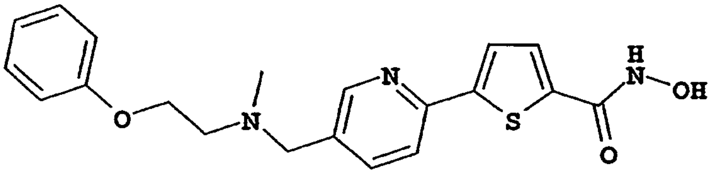


A solution of 5-(5-{[[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (130mg, 0.212mmol, Intermediate 64) in dichloromethane (3ml) was treated with 4N hydrochloric acid in dioxan (0.25ml). The solution was stirred for 18 hours, and then concentrated under reduced pressure to give a residue. The residue was crystallised from ethanol, to provide 5-(5-{[(2-hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide – hydrochloride salt (48mg) as a solid. ^{1}H

NMR [$(CD_3)_2SO$]: δ 8.72 (apparent s, 1H), 8.10 (d, 1H), 7.96 (d, 1H), 7.77 (d, 1H), 7.65 (d, 1H), 7.30 (m, 2H), 6.97 (m, 3H), 4.46 (s br, 2H), 4.39 (t br, 2H), 3.81 (t br, 2H), 3.50 (s br, 2H), 3.24 (s br, 2H). LCMS (Method A): R_T = 3.95 minutes; 414 $(M+H)^+$.

Example 22: (similarly prepared to Example 9, but using Intermediate 66)

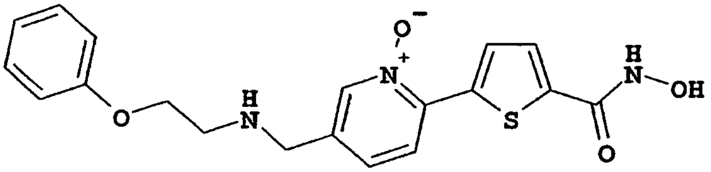
5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD_3OD): δ 8.68 (apparent s, 1H), 8.00 (dd, 1H), 7.97 (d, 1H), 7.75 (d, 1H), 7.59 (apparent s, 1H), 7.31 (m, 2H), 6.99 (m, 3H), 4.50 (s, 2H), 4.39 (t, 2H), 3.63 (apparent s, 2H), 2.97 (s, 3H). LCMS (Method A): R_T = 3.75 minutes; 384 $(M+H)^+$.

Example 23: (similarly prepared to Example 9, but using Intermediate 69)

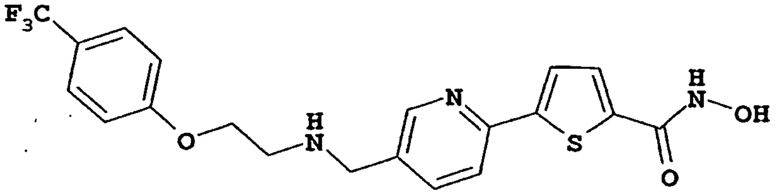
5-{1-Oxy-5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD_3OD): δ 8.59 (s, 1H), 8.38 (d, 1H), 8.10 (d, 1H), 7.72 (d, 1H), 7.68 (apparent s, 1H), 7.30 (m, 2H), 7.00 (m, 3H), 4.37 (s, 2H), 4.30 (t, 2H), 3.54 (t, 2H). LCMS (Method A): R_T = 3.32 minutes; 386 $(M+H)^+$.

Example 24: (similarly prepared to Example 14, but using Intermediate 74)

5-(5-{[2-(4-Trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide

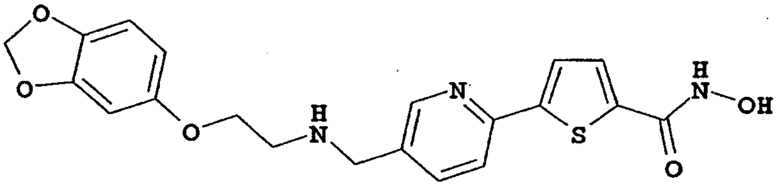


Isolated as a hydrochloride salt

^{1}H NMR (CD$_3$OD): δ 8.67 (s, 1H), 7.98 (m, 2H), 7.74 (d, 1H), 7.63 (d, 2H), 7.59 (apparent s, 1H), 7.16 (d, 2H), 4.38 (m, 4H), 3.56 (t, 2H). LCMS (Method A): R$_T$ = 4.85 minutes; 438 (M+H)$^+$.

Example 25: (similarly prepared to Example 14, but using Intermediate 77)

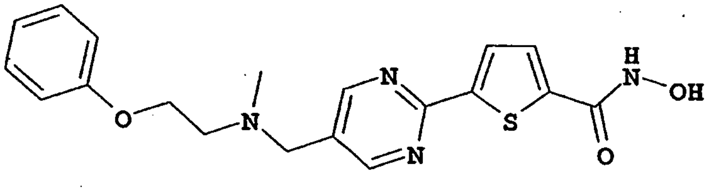
5-(5-{[2-(Benzo[1,3]dioxol-5-yloxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR (CD$_3$OD): δ 8.66 (s, 1H), 7.97 (m, 2H), 7.74 (d, 1H), 7.59 (apparent s, 1H), 6.73 (d, 1H), 6.60 (d, 1H), 6.43 (dd, 1H), 5.89 (s, 2H), 4.35 (s, 2H), 4.21 (t, 2H), 3.48 (t, 2H). LCMS (Method A): R$_T$ = 3.86 minutes; 414 (M+H)$^+$.

Example 26:

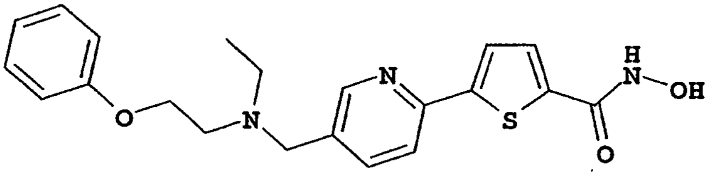
5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (210mg, 0.45mmol, Intermediate 80) in methanol (6ml) was treated with *p*-toluene sulfonic acid monohydrate (256mg, 1.3mmol). The solution was stirred at room temperature overnight, then concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with water, then dried (Na_2SO_4) and evaporated under reduced pressure to give a light brown oil. The oil was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 12:88 to 40:60, v/v, over 30 minutes) as eluent. The combined fractions were collected, concentrated and triturated with diethyl ether, to provide 5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid hydroxyamide (43mg) as a white solid. ^{1}H NMR (CD_3OD): δ 8.92 (s, 2H), 8.02 (d, 1H), 7.61 (apparent s, 1H), 7.31 (m, 2H), 7.00 (m, 3H), 4.51 (s, 2H), 4.40 (t, 2H), 3.65 (apparent s, 2H), 2.98 (s, 3H). LCMS (Method A): R_T = 3.70 minutes; 385 $(M+H)^+$.

Example 27:

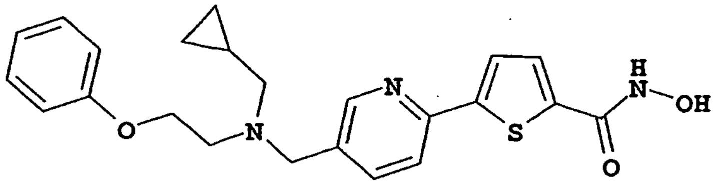
5-(5-{[Ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (507mg, 1.05mmol, Intermediate 84) in dichloromethane (20ml) was treated with 4N hydrochloric acid (1.25ml). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue, which was triturated with acetone, to provide 5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide – hydrochloride salt (310mg) as a solid. ^{1}H NMR [$(CD_3)_2SO$]: δ 11.34 (s br, 1H), 11.16 (s, 1H), 8.79 (d, 1H), 8.24 (dd, 1H), 8.08 (d, 1H), 7.87 (d, 1H), 7.66 (d br, 1H), 7.33 (m, 2H), 6.99 (m, 3H), 4.50 (d, 2H), 4.44 (t, 2H), 3.49 (m, 2H), 3.23 (m, 2H), 1.35 (t, 3H). LCMS (Method A): R_T = 4.02 minutes; 398 $(M+H)^+$.

Example 28: (similarly prepared to Example 27, but using Intermediate 88)

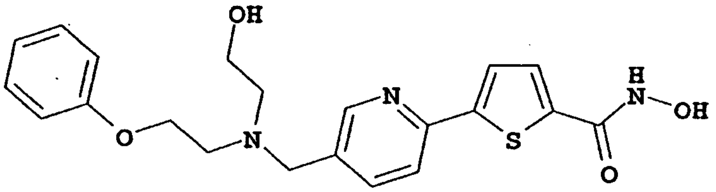
5-(5-{[Cyclopropylmethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR [$(CD_3)_2SO$]: δ 11.34 (s, 1H), 10.82 (s, 1H), 8.78 (d, 1H), 8.22 (dd, 1H), 8.08 (d, 1H), 7.87 (d, 1H), 7.65 (d br, 1H), 7.33 (m, 2H), 6.99 (m, 3H), 4.57 (m, 2H), 4.44 (m, 2H), 3.54 (m, 2H), 3.15 (t, 2H), 1.25 (m, 1H), 0.68 (m, 2H), 0.44 (m, 2H). LCMS (Method A): R_T = 4.46 minutes; 424 $(M+H)^+$.

Example 29:

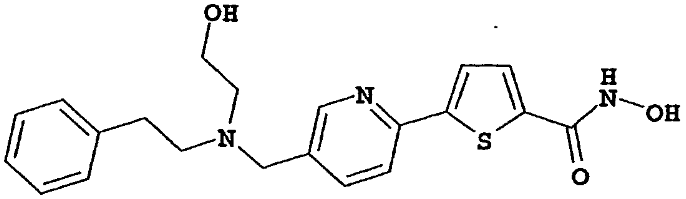
5-(5-{[(2-Hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



A solution of 5-(5-{[[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (130mg, 0.212mmol, Intermediate 91) in dichloromethane (3ml) was treated with 4N hydrochloric acid (0.25ml). The solution was stirred at room temperature overnight, and then concentrated under reduced pressure to give a residue, which was triturated with ethanol:diethyl ether (1:2), to provide 5-(5-{[(2-hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide – hydrochloride salt (48mg) as a solid. ^{1}H NMR [$(CD_3)_2SO$]: δ 11.0 (s br, 1H), 8.72 (s, 1H), 8.10 (d, 1H), 7.96 (d, 1H), 7.77 (d, 1H), 7.65 (d, 1H), 7.30 (m, 2H), 6.97 (m, 3H), 4.46 (s, 2H), 4.39 (apparent t br, 2H), 3.81 (apparent t br, 2H), 3.50 (s, 2H), 3.23 (s, 2H). LCMS (Method A): R_T = 3.95 minutes; 414 $(M+H)^+$.

Example 30: (similarly prepared to Example 27, but using Intermediate 93)

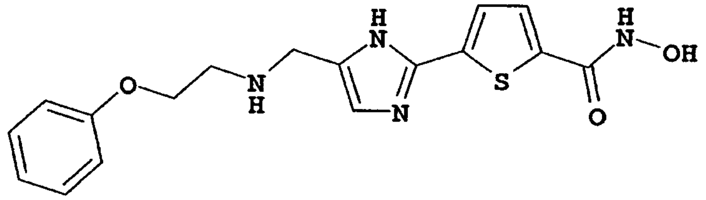
5-(5-{[(2-Hydroxy-ethyl)-phenethyl-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR [$(CD_3)_2SO$]: δ 11.34 (s br, 1H), 10.84 (s, 1H), 8.79 (d, 1H), 8.23 (dd, 1H), 8.08 (d, 1H), 7.87 (d, 1H), 7.66 (d br, 1H), 7.34 (m, 2H), 7.26 (m, 3H), 4.55 (m, 2H), 3.86 (m, 2H), 3.34 (m, 2H), 3.25 (m, 2H), 3.15 (m, 2H). LCMS (Method A): R_T = 3.81 minutes; 398 $(M+H)^+$.

Example 31:

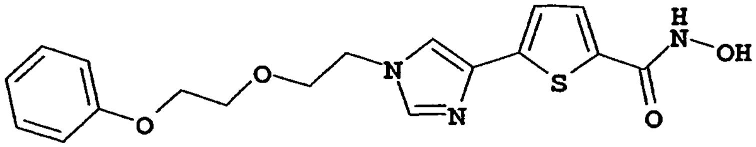
5-{5-[(2-Phenoxy-ethylamino)-methyl]-1*H*-imidazol-2-yl}-thiophene-2-carboxylic acid hydroxyamide



To a solution of (2-phenoxy-ethyl)-[2-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-ylmethyl]-carbamic acid *tert*-butyl ester (77mg, 0.114mmol, Intermediate 97) and methanol (3ml) was added 4N hydrochloric acid in dioxane solution (1ml). The resultant reaction mixture was heated at 100°C for 2 hours, and then allowed to cool to give a precipitated solid. The solid was filtered and washed with cold dioxane and dried under vacuum at 60°C, to provide 5-{5-[(2-phenoxy-ethylamino)-methyl]-1*H*-imidazol-2-yl}-thiophene-2-carboxylic acid hydroxyamide (24mg) as a solid. ^{1}H NMR [$(CD_3)_2SO$]: δ 11.38 (s, 1H), 9.38 (s, 2H), 7.69 (d, 1H), 7.64 (apparent s, 1H), 7.51 (s, 1H), 7.32 (m, 2H), 6.99 (m, 3H), 4.28 (t, 2H), 4.23 (apparent s, 2H), 3.57 (s, 3H), 3.40 (apparent s, 2H). LCMS (Method A): R_T = 3.22 minutes; 359 $(M+H)^+$.

Example 32: (similarly prepared to Example 15, but using Intermediate 105)

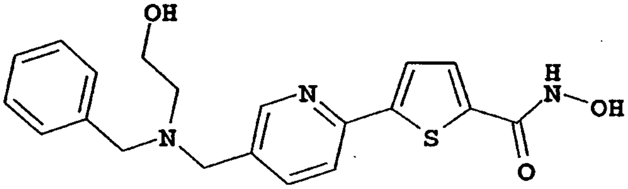
5-{1-[2-(2-Phenoxy-ethoxy)-ethyl]-1*H*-imidazol-4-yl}-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR [$(CD_3)_2SO$]: δ 11.40 (s br, 1H), 8.95 (s, 1H), 8.06 (s, 1H), 7.64 (apparent s, 1H), 7.56 (d, 1H), 7.25 (m, 2H), 6.90 (m, 3H), 4.35 (t, 2H), 4.07 (m, 2H), 3.89 (t, 2H), 3.79 (m, 2H). LCMS (Method A): R_T = 4.35 minutes; 374 $(M+H)^+$.

Example 33: (similarly prepared to Example 29, but using Intermediate 110)

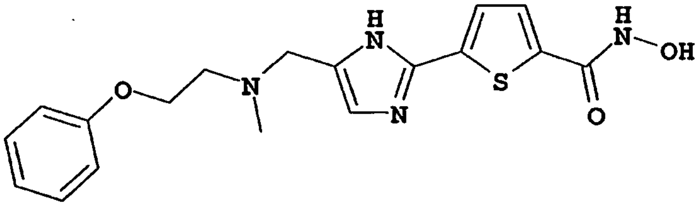
5-(5-{[Benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR [$(CD_3)_2SO$]: δ 11.35 (s br, 1H), 10.94 (s, 1H), 8.74 (d, 1H), 8.20 (dd, 1H), 8.06 (d, 1H), 7.87 (d, 1H), 7.66 (m, 3H), 7.46 (m, 3H), 4.42 (m, 4H), 3.81 (q, 2H), 3.04 (apparent t, 2H). LCMS (Method A): R_T = 3.47 minutes; 384 $(M+H)^+$.

Example 34: (similarly prepared to Example 1, but using Intermediate 113)

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-1*H*-imidazol-2-yl)-thiophene-2-carboxylic acid hydroxyamide



^{1}H NMR [$(CD_3)_2SO$]: δ 7.89 (d, 1H), 7.85 (s, 1H), 7.74 (d br, 1H), 7.34 (m, 2H), 7.02 (m, 3H), 4.55 (s, 2H), 4.43 (t, 2H), 3.64 (apparent br s, 2H), 2.94 (s, 3H). LCMS (Method B): R_T = 1.66 minutes; 373 $(M+H)^+$.

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Intermediate 1:

5-[5-(2-Benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid methyl ester

A solution of 5-(5-amino-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (64mg, 0.27mmol, Intermediate 2) and benzyloxyacetaldehyde (43mg, 0.28mmol) in anhydrous tetrahydrofuran (3.4ml), was stirred for 60 hours. Glacial acetic acid (14µl, 0.23mmol) and sodium triacetoxyborohydride (86mg, 0.4mmol) were then added to the reaction mixture. After stirring for a further 24 hours the reaction mixture was concentrated. The residue was dissolved in ethyl acetate and the resultant solution washed with 10% citric acid solution, followed by saturated sodium hydrogen carbonate solution, then brine. The organic layer was separated, dried ($MgSO_4$) and evaporated to give a residue, which was subjected to flash column chromatography using a mixture of cyclohexane and ethyl acetate (gradient 80:20 to 70:30, v/v) as eluent, to provide 5-[5-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid methyl ester (70mg) as a yellow solid. LCMS (Method B): $R_T = 3.76$ minutes; 369 $(M+H)^+$.

Intermediate 2:

5-(5-Amino-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester

A suspension of 5-(5-nitro-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (1.78g, 6.7mmol, Intermediate 3), palladium (5 wt. % on activated carbon) (500mg) and acetonitrile (300ml) was stirred under a hydrogen atmosphere for 90 minutes. The mixture was then filtered through Hyflo, and the filtrate was concentrated *in vacuo*, to provide 5-(5-amino-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (1.40g) as a yellow solid. LCMS (Method B): $R_T = 2.54$ minutes; 235 $(M+H)^+$.

Intermediate 3:

5-(5-Nitro-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester

To a suspension of 5-(5-nitro-pyridin-2-yl)-thiophene-2-carboxylic acid (2.25g, 9.0mmol, Intermediate 4) in methanol (50ml) at $60^{O}C$, was added concentrated hydrochloric acid (2ml). The reaction mixture was stirred and heated at reflux for 48 hours, and then concentrated to give a yellow powder. The yellow powder was basified using sodium carbonate solution and aqueous sodium hydroxide solution and collected by filtration, to provide 5-(5-nitro-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (1.78g) as a solid. LCMS (Method C): $R_T = 3.56$ minutes.

Intermediate 4:

5-(5-Nitro-pyridin-2-yl)-thiophene-2-carboxylic acid

Acetonitrile (50mL) and a solution of 0.4 M aqueous sodium carbonate solution (50ml) were degassed (*via* nitrogen purge), then combined under a nitrogen atmosphere. 2-Bromo-5-nitropyridine (3.48g, 17.0mmol) and 5-(dihydroxyboryl)-2-thiophenecarboxylic acid (2.96g, 17.0mmol) were added to the solution, which was heated to 90^{O}C, followed by the addition of tetrakis(triphenylphosphine)palladium(0) (0.98g, 0.85mmol). After stirring overnight the reaction mixture was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The aqueous layer was separated and acidified with concentrated hydrochloric acid to give a green precipitate, which was collected and then washed with water, dichloromethane, and chloroform to provide 5-(5-nitro-pyridin-2-yl)-thiophene-2-carboxylic acid (2.45g). LCMS (Method C): $R_T = 2.97$ minutes.

Intermediate 5:

5-{1-[2-(2-Phenoxy-ethoxy)-ethyl]-1*H*-pyrazol-3-yl}-thiophene-2-carboxylic acid methyl ester

To a mixture of 5-(1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester (100mg, 0.48mmol, Intermediate 6), potassium carbonate (300mg, 2.18mmol) and *N,N*-dimethylformamide (2ml) was added 1-(2-chloroethoxy)-2-phenoxyethane (96mg, 0.48mmol). The resulting mixture was heated to 80^{O}C and stirred overnight. Water (4ml) was added to the reaction mixture, which was allowed to stir for a further 30 minutes, before being extracted with ethyl acetate (2x). The combined organic layers were evaporated to dryness, to provide 5-{1-[2-(2-phenoxy-ethoxy)-ethyl]-1*H*-pyrazol-3-yl}-thiophene-2-carboxylic acid methyl ester which was used directly without further purification. LCMS (Method B): $R_T = 3.75$ minutes; 373 $(M+H)^+$.

Intermediate 6:

5-(1*H*-Pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester

A suspension of 5-(1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid (1.09g, 9.0mmol, Intermediate 7) in methanol (30ml) and concentrated hydrochloric acid (1.32ml), was heated to reflux overnight. The reaction mixture was concentrated to give a residue, which was partitioned between saturated aqueous sodium hydrogen carbonate solution and dichloromethane. The organic phase was separated and concentrated, to provide 5-(1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester (1.04g) as a beige solid, which was used directly without further purification.

Intermediate 7:

5-(1*H*-Pyrazol-3-yl)-thiophene-2-carboxylic acid

A suspension of 5-(1*H*-pyrazol-3-yl)-thiophene-2-carbonitrile (90mg, 0.51mmol, Intermediate 8) in sodium hydroxide solution (15ml, 1M) was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature, diluted with water, acidified with hydrochloric acid (1M) and extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate and then evaporated under reduced pressure. The residue was subjected to flash column chromatography to provide 5-(1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid (97mg, 97%) as a yellow solid. LCMS (Method A): R_T = 4.79 minutes; 195 $(M+H)^+$.

Intermediate 8:

5-(1*H*-Pyrazol-3-yl)-thiophene-2-carbonitrile

A solution of 5-(3-dimethylamino-acryloyl)-thiophene-2-carbonitrile (1.19g, 5.77mmol) in ethanol (20ml) was treated with hydrazine hydrate (0.20ml, 6.4mmol). The mixture was heated to reflux for 16 hours and then partitioned between ethyl acetate and water. The organic layer was isolated and concentrated under reduced pressure, to provide 5-(1*H*-pyrazol-3-yl)-thiophene-2-carbonitrile (0.80g) as a brown solid. LCMS (Method A): R_T = 5.90 minutes; 176 $(M+H)^+$.

Intermediate 9:

5-{6-[(2-Phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

A solution of 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (272mg, 0.87mmol, Intermediate 10) in *N,N*-dimethylformamide (3ml) was treated with diisopropylethylamine (107µl, 0.62mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (42mg, 0.36mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (126mg, 0.33mmol). The mixture was stirred at room temperature for 3 hours, then diluted with water, and extracted with ethyl acetate

(3x). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure, to provide 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (168mg) as a brown viscous oil. LCMS (Method B): R_T = 2.26 minutes; 454 $(M+H)^+$.

Intermediate 10:

5-{6-[(2-Phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid

A mixture of 5-(6-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid (75mg, 0.32mmol, Intermediate 11), 2-phenoxyethylamine (44mg, 0.32mmol), and anhydrous ethanol (4ml), was stirred at room temperature for 1 hour, and then sodium borohydride (20mg, 0.53mmol) was added. After stirring overnight the reaction mixture was concentrated, to provide 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid as a solid, which was used directly without further purification. LCMS (Method B): R_T = 2.10 minutes; 355 $(M+H)^+$.

Intermediate 11:

5-(6-Formyl-pyridin-2-yl)-thiophene-2-carboxylic acid

Acetonitrile (125mL) and a solution of 0.4 M aqueous sodium carbonate (125mL) were degassed (*via* nitrogen purge), then combined under a nitrogen atmosphere. 2-Bromopyridine-6-carboxaldehyde (5.6g, 30mmol) and 5-(dihydroxyboryl)-2-thiophenecarboxylic acid (4.3g, 25mmol) were added to the solution, which was heated to 80°C, followed by the addition of tetrakis(triphenylphosphine)palladium(0) (585mg, 0.51mmol). After stirring at 80°C for 1 hour the reaction mixture was partitioned between ethyl acetate and saturated ammonium chloride solution. The aqueous layer was isolated and acidified with 1M hydrochloric acid to give a white solid which was collected by filtration, and dried under vacuum, to provide 5-(6-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid (4.29g) as a white solid. LCMS (Method B): R_T = 2.75 minutes; 233 $(M)^+$.

Intermediate 12: (similarly prepared to Intermediate 10, but using *N*-1-[3-(3-aminopropoxy)phenyl]acetamide)

5-(6-{[3-(3-Acetylamino-phenoxy)-propylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 1.92$ minutes; 426 $(M+H)^+$.

Intermediate 13: (similarly prepared to Intermediate 10, but using *N*-benzyl-*N*-(2-dimethylaminoethyl)amine

5-(6-{[Benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 2.15$ minutes; 396 $(M+H)^+$.

Intermediate 14: (similarly prepared to Intermediate 9, but using Intermediate 15)

5-{5-[(2-Phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): $R_T = 2.14$ minutes; 454 $(M+H)^+$.

Intermediate 15:

5-{5-[(2-Phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid

To a mixture of 5-(5-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid (66mg, 0.28mmol, Intermediate 16), 2-phenoxyethylamine (38mg, 0.28mmol), and dichloroethane (4ml), was added sodium triacetoxyborohydride (60mg, 0.28mmol). After stirring overnight the reaction mixture was concentrated, to provide 5-{5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid as yellow solid, which was used directly without further purification. LCMS (Method B): $R_T = 2.01$ minutes; 355 $(M+H)^+$.

Intermediate 16: (similarly prepared to Intermediate 11, but using 2-bromopyridine-5-carboxaldehyde)

5-(5-Formyl-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 2.57$ minutes; 233 $(M)^+$.

Intermediate 17: (similarly prepared to Intermediate 9, but using Intermediate 18)

5-[6-(2-Benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): $R_T = 3.43$ minutes; 454 $(M+H)^+$.

Intermediate 18:

5-[6-(2-Benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid

A mixture of 5-(6-amino-pyridin-2-yl)-thiophene-2-carboxylic acid (400mg, 1.8mmol, Intermediate 19) and benzyloxyacetaldehyde (354mg, 2.4mmol), in dichloroethane (6ml), was stirred for 5 minutes. Sodium triacetoxyborohydride (763mg, 3.6mmol) was then added to the reaction mixture, which was stirred overnight. The reaction mixture was concentrated to give a residue, which was subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 5:95 to 5:95, v/v, over 90 minutes) as eluent, to provide 5-[6-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid (280mg). LCMS (Method B): $R_T = 3.29$ minutes; 355 $(M+H)^+$.

Intermediate 19: (similarly prepared to Intermediate 11, but using 2-amino-6-bromopyridine)

5-(6-Amino-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 1.53$ minutes; 221 $(M+H)^+$.

Intermediate 20:

5-{6-[(2-Phenoxy-ethylamino)-methyl]-pyridin-3-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

A solution of 5-(6-{[*tert*-butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-thiophene-2-carboxylic acid (413mg, 0.91mmol, Intermediate 21) in *N,N*-dimethylformamide (6ml) was treated with *N,N*-diisopropylethylamine (317µl, 1.8mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (107mg, 0.91mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (346mg, 0.91mmol). The mixture was stirred at room temperature overnight, then diluted with water, and extracted with ethyl acetate (3x). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue which was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (60:40, v/v) as eluent, to provide 5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-3-yl}-

thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (196mg) as a brown foam. This was used without further purification.

Intermediate 21: (similarly prepared to Intermediate 11, but using Intermediate 22)

5-(6-{[*tert*-Butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-3-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 3.76$ minutes; 455 $(M+H)^+$.

Intermediate 22:

(5-Bromo-pyridin-2-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester

To a solution of 5-bromo-pyridine-2-carbaldehyde (800mg, 4.3mmol, Intermediate 23) in ethanol (15ml) was added 2-(phenoxy)-ethylamine (594mg, 4.3mmol). After stirring overnight, sodium borohydride (162mg, 4.3mmol) was added to the solution and the resultant mixture was allowed to stir for a further hour before being concentrated under reduced pressure to give a residue. The residue was dissolved in dichloromethane (20ml) to which *N,N*-diisopropylethylamine (1.25ml, 7.1mmol) followed by di-*tert*-butyldicarbonate (1.5g, 6.9mmol) were added. After stirring for an hour the reaction mixture was washed with saturated sodium hydrogen carbonate solution. The organic layer was isolated, dried (Na_2SO_4) and concentrated to give a brown oil which was subjected to silica-gel column chromatography using ethyl acetate and cyclohexane (gradient 0:100 to 25:75, v/v) as eluent, to provide (5-bromo-pyridin-2-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester (395mg). LCMS (Method B): $R_T = 4.27$ minutes; 407 & 409 $(M+H)^+$.

Intermediate 23:

5-Bromo-pyridine-2-carbaldehyde

To a cooled (-78°C) solution of 2,5-dibromopyridine (1.5mg, 6.3mmol) in dry toluene (75ml) under nitrogen atmosphere was slowly added *n*-butyl lithium (3.0ml, 7.5mmol). After stirring at –78°C for 2 hours *N,N*-dimethylformamide (640µl, 9.5mmol) was slowly added to the reaction mixture which was allowed to stir for 1 hour before being warmed to 0°C. Saturated ammonium chloride solution was then added to the reaction mixture which was vigourously stirred for 15 minutes, forming a suspension which was extracted with diethyl ether. The organic layer was isolated, dried (Na_2SO_4), and concentrated, to provide

5-bromo-pyridine-2-carbaldehyde (802mg) as a brown oily solid. This was used without further purification.

Intermediate 24:

{6-[5-(Tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-[2-(3-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

A solution of 5-[5-({*tert*-butoxycarbonyl-[2-(3-trifluoromethyl-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid (140mg, 0.27mmol, Intermediate 25) in *N,N*-dimethylformamide (3ml) was treated with *N,N*-diisopropylethylamine (92µl, 0.54mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (35mg, 0.30mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (112mg, 0.30mmol). The mixture was stirred at room temperature overnight, then diluted with water, and extracted with ethyl acetate (3x). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue which was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (60:40, v/v) as eluent, to provide {6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-[2-(3-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester (134mg) as a colourless waxy solid. LCMS (Method B): R_T = 4.24 minutes; 622 $(M+H)^+$.

Intermediate 25:

5-[5-({*tert*-Butoxycarbonyl-[2-(3-trifluoromethyl-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

A mixture of 5-(5-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid (150mg, 0.64mmol, Intermediate 16), 2-(3-trifluoromethyl-phenoxy)-ethylamine (155mg, 0.64mmol) and *N,N*-diisopropylethylamine (109µl, 0.64mmol) in ethanol (10ml) was stirred for 2 hours, before sodium borohydride (24mg, 0.64mmol) was added. After stirring for a further 2 hours, the reaction mixture was concentrated to give a residue. Di-*tert*-butyldicarbonate (167mg, 0.77mmol) and *N,N*-diisopropylethylamine (131µl, 0.77mmol) in *N,N*-dimethylformamide (10ml) were added to the residue. After stirring overnight the reaction mixture was partitioned between ethyl acetate and 1M hydrochloric acid. The organic layer was isolated, dried ($MgSO_4$) and concentrated, to provide 5-[5-({*tert*-butoxycarbonyl-[2-(3-

trifluoromethyl-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid (140mg) as a yellow oil. LCMS (Method B): $R_T = 4.14$ minutes; 523 $(M+H)^+$.

Intermediate 26: (similarly prepared to Intermediate 24, but using Intermediate 27)

[2-(4-Methoxy-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 3.92$ minutes; 584 $(M+H)^+$.

Intermediate 27: (similarly prepared to Intermediate 25, but using 2-[4-methoxy-phenoxy]-ethylamine)

5-[5-({*tert*-Butoxycarbonyl-[2-(4-methoxy-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 3.81$ minutes; 485 $(M+H)^+$.

Intermediate 28: (similarly prepared to Intermediate 24, but using Intermediate 29)

[2-(2-Chloro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.15$ minutes; 588 & 590 $(M+H)^+$.

Intermediate 29: (similarly prepared to Intermediate 25, but using 2-[2-chloro-phenoxy]-ethylamine)

5-[5-({*tert*-Butoxycarbonyl-[2-(2-chloro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 4.05$ minutes; 489 & 491 $(M+H)^+$.

Intermediate 30: (similarly prepared to Intermediate 24, but using Intermediate 31)

[2-(4-Fluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.00$ minutes; 572 $(M+H)^+$.

Intermediate 31:

5-[5-({*tert*-Butoxycarbonyl-[2-(4-fluoro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

Acetonitrile (2.5mL) and a solution of 0.4 M aqueous sodium carbonate solution (2.5ml) were degassed (*via* nitrogen purge), then combined under a nitrogen atmosphere. (6-Bromo-pyridin-3-ylmethyl)-[2-(4-fluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester (133mg, 0.31mmol, Intermediate 32) and 5-(dihydroxyboryl)-2-thiophenecarboxylic acid (73mg, 0.62mmol) were added to the solution, which was heated to 90^{O}C, followed by the addition of tetrakis(triphenylphosphine)palladium(0) (7mg, 2mol%). After stirring for 4 hours the reaction mixture was partitioned between ethyl acetate and 1M hydrochloric acid. The organic layer was isolated, dried ($MgSO_4$) and concentrated, to provide 5-[5-({*tert*-butoxycarbonyl-[2-(4-fluoro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid (150mg) as an oil. LCMS (Method B): R_T = 3.89 minutes; 473 $(M+H)^+$.

Intermediate 32:

(6-Bromo-pyridin-3-ylmethyl)-[2-(4-fluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

To a solution of 4-fluorophenol (101mg, 0.90mmol), (6-bromo-pyridin-3-ylmethyl)-(2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (200mg, 0.60mmol, Intermediate 33) and triphenylphosphine (236mg, 0.90mmol) was added diethyldiazocarboxylate (143μl, 0.90mmol). The reaction mixture was subsequently heated to reflux for 2.5 hours, before being cooled and diluted with ethyl acetate. The organic layer was isolated, washed with 1M hydrochloric acid, followed by saturated sodium hydrogen carbonate solution, then water, and then dried ($MgSO_4$) and concentrated to give a residue. The residue was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (gradient, 95:5 to 85:15, v/v, over 20 minutes) as eluent, to provide (6-bromo-pyridin-3-ylmethyl)-[2-(4-fluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester (133mg). LCMS (Method B): R_T = 4.20 minutes; 425 & 427 $(M+H)^+$.

Intermediate 33:

(6-Bromo-pyridin-3-ylmethyl)-(2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester

A mixture of 2-bromo-pyridine-5-carbaldehyde (1.5g, 8.0mmol) and ethanolamine (935μl, 15.1mmol) in ethanol (10ml) was stirred overnight. Sodium borohydride (332mg, 8.8mmol) was added portionwise and the mixture stirred for 1.5 hours. The reaction mixture was quenched with water, acidified with 1M hydrochloric acid and washed with ethyl acetate. The aqueous layer was subsequently neutralised with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil (1.7g). The oil was dissolved in dichloromethane (10ml), to which *N,N*-diisopropylethylamine (1.37ml, 8.0mmol) followed by di-*tert*-butyldicarbonate (1.8g, 8.0mmol) was added. After stirring overnight, the reaction mixture was washed with 1M hydrochloric acid and the organic layer was separated, dried ($MgSO_4$) and concentrated, to provide (6-bromo-pyridin-3-ylmethyl)-(2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (2.5g) as a yellow oil. LCMS (Method B): $R_T = 2.95$ minutes; 331 & 333 $(M+H)^+$.

Intermediate 34: (similarly prepared to Intermediate 24, but using Intermediate 35)
[2-(3-Methoxy-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 3.96$ minutes; 584 $(M+H)^+$.

Intermediate 35: (similarly prepared to Intermediate 31, but using Intermediate 36)
5-[5-({*tert*-Butoxycarbonyl-[2-(3-methoxy-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 3.85$ minutes; 485 $(M+H)^+$.

Intermediate 36: (similarly prepared to Intermediate 32, but using 3-methoxyphenol)
(6-Bromo-pyridin-3-ylmethyl)-[2-(3-methoxy-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.17$ minutes; 437 & 439 $(M+H)^+$.

Intermediate 37: (similarly prepared to Intermediate 24, but using Intermediate 38)
[2-(3-Fluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.03$ minutes; 572 $(M+H)^+$.

Intermediate 38: (similarly prepared to Intermediate 31, but using Intermediate 39)

5-[5-({*tert*-Butoxycarbonyl-[2-(3-fluoro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): R_T = 3.92 minutes; 473 $(M+H)^+$.

Intermediate 39: (similarly prepared to Intermediate 32, but using 3-fluorophenol)

(6-Bromo-pyridin-3-ylmethyl)-[2-(3-fluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.24 minutes; 425 & 427 $(M+H)^+$.

Intermediate 40: (similarly prepared to Intermediate 24, but using Intermediate 41)

[2-(2,6-Difluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.05 minutes; 590 $(M+H)^+$.

Intermediate 41: (similarly prepared to Intermediate 31, but using Intermediate 42)

5-[5-({*tert*-Butoxycarbonyl-[2-(2,6-difluoro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): R_T = 3.95 minutes; 491 $(M+H)^+$.

Intermediate 42: (similarly prepared to Intermediate 32, but using 2,6-difluorophenol)

(6-Bromo-pyridin-3-ylmethyl)-[2-(2,6-difluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.26 minutes; 443 & 445 $(M+H)^+$.

Intermediate 43: (similarly prepared to Intermediate 24, but using Intermediate 44)

[2-(2,5-Difluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.02 minutes; 590 $(M+H)^+$.

Intermediate 44: (similarly prepared to Intermediate 31, but using Intermediate 45)

5-[5-({*tert*-Butoxycarbonyl-[2-(2,5-difluoro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 3.92$ minutes; 491 $(M+H)^+$.

Intermediate 45: (similarly prepared to Intermediate 32, but using 2,5-difluorophenol)

(6-Bromo-pyridin-3-ylmethyl)-[2-(2,5-difluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.23$ minutes; 443 & 445 $(M+H)^+$.

Intermediate 46: (similarly prepared to Intermediate 24, but using Intermediate 47)

[2-(2,6-Dichloro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.34$ minutes; 622, 624 & 626 $(M+H)^+$.

Intermediate 47: (similarly prepared to Intermediate 31, but using Intermediate 48)

5-[5-({*tert*-Butoxycarbonyl-[2-(2,6-dichloro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 4.26$ minutes; 523, 525 & 527 $(M+H)^+$.

Intermediate 48: (similarly prepared to Intermediate 32, but using 2,6-dichlorophenol)

(6-Bromo-pyridin-3-ylmethyl)-[2-(2,6-dichloro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.60$ minutes; 475, 477 & 479 $(M+H)^+$.

Intermediate 49: (similarly prepared to Intermediate 24, but using Intermediate 50)

[2-(2,4-Difluoro-phenoxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.03$ minutes; 590 $(M+H)^+$.

Intermediate 50: (similarly prepared to Intermediate 31, but using Intermediate 51)

5-[5-({*tert*-Butoxycarbonyl-[2-(2,4-difluoro-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 3.92$ minutes; 491 $(M+H)^+$.

Intermediate 51: (similarly prepared to Intermediate 32, but using 2,4-difluorophenol)

(6-Bromo-pyridin-3-ylmethyl)-[2-(2,4-difluoro-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.23$ minutes; 443 & 445 $(M+H)^+$.

Intermediate 52: (similarly prepared to Example 1, but using Intermediate 53)

[2-(5-Hydroxycarbamoyl-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 3.38$ minutes; 471 $(M+H)^+$.

Intermediate 53:

5-(5-{[*tert*-Butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid methyl ester

A stirred solution of [2-(5-bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester (210mg, 0.43mmol, Intermediate 54), palladium (II) acetate (17mg, 0.076mmol), 1,3-bis(diphenylphosphino)propane (15mg, 0.036mmol), triethylamine (150µl, 1.1mmol), dry *N,N*-dimethylformamide (5ml) and methanol (3.5ml) was purged with carbon monoxide gas for 10 minutes. The reaction mixture was then heated at 70^{O}C under a carbon monoxide atmosphere overnight, before being diluted with water. The resultant mixture was extracted with ethyl acetate (x2), and the organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated to give a brown oil. The oil was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (gradient, 100:0 to 95:5 to 90:10, v/v) as eluent, to provide 5-(5-{[*tert*-butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid methyl ester (136mg) as a light brown oil. LCMS (Method B): $R_T = 4.40$ minutes; 470 $(M+H)^+$.

Intermediate 54:

[2-(5-Bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester

To a solution of [2-(5-bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-amine (0.48g, 1.2mmol, Intermediate 55) and *N,N*-diisopropylethylamine (315µl, 1.8mmol) in dry dichloromethane (15ml) was added di-*tert*-butyldicarbonate (294mg, 1.3mmol). After stirring overnight the reaction mixture was concentrated to give a residue, which was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (gradient, 90:10 to 85:15v/v) as eluent, to provide [2-(5-bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester (511mg). LCMS (Method B): $R_T = 4.77$ minutes; 490 & 492 $(M+H)^+$.

Intermediate 55:

[2-(5-Bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-amine

To a solution of 2-(5-bromo-thiophen-2-yl)-pyrimidine-5-carbaldehyde (303mg, 1.07mmol, Intermediate 56) and 2-phenoxyethylamine (137mg, 1.0mmol) in dichloroethane (10ml) was added sodium triacetoxyborohydride (254mg, 1.2mmol). After stirring overnight the reaction mixture was washed with saturated sodium hydrogen carbonate solution, and the organic layer was isolated and concentrated to give a residue. The residue was dissolved in methanol, passed over a SCX-2 ion exchange cartridge, and the resultant solution was concentrated, to provide [2-(5-bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-(2-phenoxy-ethyl)-amine (241mg) as a brown solid. LCMS (Method B): $R_T =$ 2.38 minutes; 390 & 392 $(M+H)^+$.

Intermediate 56:

2-(5-Bromo-thiophen-2-yl)-pyrimidine-5-carbaldehyde

To an orange suspension of 5-diethoxymethyl-2-thiophen-2-yl-pyrimidine (4.22g, 16.0mmol, Intermediate 57) in glacial acetic acid (50ml) was added *N*-bromosuccinimide (2.89g, 16.2mmol). After stirring for 1 hour, water was added to the mixture, which was subsequently stirred for a further 30 minutes and extracted with ethyl acetate (4x). The organic layers were combined and washed with water, followed by brine, then dried (Na_2SO_4), and concentrated to give a brown solid. The brown solid was triturated with diethyl ether, collected by filtration, and dried under vacuum, to provide 2-(5-bromo-thiophen-2-yl)-pyrimidine-5-carbaldehyde (2.87g) as a fine brown powder. LCMS (Method B): $R_T = 3.20$ minutes; 269 & 271 $(M+H)^+$.

Intermediate 57:

5-Diethoxymethyl-2-thiophen-2-yl-pyrimidine

To a solution of triformylmethane (0.60g, 6.0mmol) in dry ethanol (75ml) was added thiophene-2-carboximidamide hydrochloride (1.17g, 7.2mmol). After stirring for 45 minutes at room temperature, the solution was heated at reflux overnight before being cooled to room temperature and concentrated, to provide 5-diethoxymethyl-2-thiophen-2-yl-pyrimidine as an oily orange solid. This was used without further purification.

Intermediate 58: (similarly prepared to Intermediate 24, but using Intermediate 59)

5-(1-{2-[Benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): $R_T = 0.36$ minutes; 515 $(M+H)^+$.

Intermediate 59:

Lithium; 5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylate

To a solution of 5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester (340mg, 0.79mmol, Intermediate 60) in acetonitrile (12ml) was added 2M lithium hydroxide solution (2ml, 3.96mmol) and water (2ml). After stirring for 72 hours the mixture was concentrated to provide lithium; 5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylate as a residue, which was used without further purification. LCMS (Method B): $R_T = 2.00$ minutes; 416 $(M+H)^+$.

Intermediate 60:

5-(1-{2-[Benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester

To a solution of 5-(1-{2-[(benzo[1,3]dioxol-5-ylmethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2 carboxylic acid methyl ester (384mg, 1.0mmol, Intermediate 61) and 2-

bromoethanol (2ml, 28.0mmol) in acetonitrile (5ml) was added potassium carbonate (415mg, 3.0mmol), and the resulting mixture was heated to 70°C. After stirring overnight at 70°C the reaction mixture was quenched with water and extracted with diethyl ether. The organic layer was isolated, dried ($MgSO_4$) and concentrated to give a residue, which was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (gradient, 100:0 to 90:10 to 0:100, v/v) as eluent, to provide 5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester (343mg) as an oil. LCMS (Method B): R_T = 2.15 minutes; 430 $(M+H)^+$.

Intermediate 61:

5-(1-{2-[(Benzo[1,3]dioxol-5-ylmethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2 carboxylic acid methyl ester

A solution of 5-[1-(3-amino-ethyl)-1*H*-pyrazol-3-yl]-thiophene-2-carboxylic acid methyl ester (100mg, 0.4mmol, Intermediate 62) and piperonal (50mg, 0.33mmol) in anhydrous methanol (3ml) was stirred overnight. Sodium borohydride (19mg, 0.5mmol) was then added to the reaction mixture, which was stirred for a further 2 hours before being concentrated. The residue was treated with water (2ml) and saturated sodium hydrogen carbonate solution (1ml) then loaded onto an Isolute® HM-N cartridge (5ml). After 30 minutes the cartridge was washed with chloroform and the solvent concentrated, to provide 5-(1-{2-[(benzo[1,3]dioxol-5-ylmethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester. LCMS (Method B): R_T = 2.20 minutes; 386 $(M+H)^+$.

Intermediate 62:

5-[1-(2-Amino-ethyl)-1*H*-pyrazol-3-yl]-thiophene-2-carboxylic acid methyl ester

To a cooled (0°C) solution of 5-[1-(3-*tert*-butoxycarbonylamino-ethyl)-1*H*-pyrazol-3-yl]-thiophene-2-carboxylic acid methyl ester (137mg, 0.4mmol, Intermediate 63) in dichloromethane (2.5ml), was added trifluoroacetic acid (2.5ml). The reaction mixture was stirred for 2 hours then concentrated to give a residue, which was partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The aqueous layer was further extracted with dichloromethane (x2) and the organic layers were combined, dried ($MgSO_4$) and concentrated, to provide 5-[1-(2-amino-ethyl)-1*H*-pyrazol-3-yl]-

thiophene-2-carboxylic acid methyl ester (73mg) as a yellow oil. LCMS (Method B): R_T = 1.78 minutes; 252 $(M+H)^+$.

Intermediate 63:

5-[1-(2-*tert*-Butoxycarbonylamino-ethyl)-1*H*-pyrazol-3-yl]-thiophene-2-carboxylic acid methyl ester

To a mixture of 5-(1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid methyl ester (1.17g, 5.0mmol, Intermediate 6), potassium carbonate (2.08g, 15.0mmol) and *N,N*-dimethylformamide (30ml) was added 2-(*tert*-butoxycarbonylamino)ethyl bromide (1.26g, 5.5mmol). The resulting mixture was heated to 70°C and stirred overnight. The reaction mixture was concentrated to remove excess solvent, then partitioned between ethyl acetate and water. The organic layer was isolated, and the aqueous layer extracted with ethyl acetate (2x). The combined organic layers were evaporated to dryness, to provide 5-[1-(2-*tert*-butoxycarbonylamino-ethyl)-1*H*-pyrazol-3-yl]-thiophene-2-carboxylic acid methyl ester (1.44g) as a pale yellow solid. LCMS (Method B): R_T = 3.33 minutes; 352 $(M+H)^+$.

Intermediate 64: (similarly prepared to Intermediate 24, but using Intermediate 65)

5-(5-{[[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): R_T = 3.14 minutes; 612 $(M+H)^+$.

Intermediate 65:

5-(5-{[[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

To a solution of 5-{5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (300mg, 0.84mmol, Intermediate 15), (*tert*-butyldimethylsilyloxy)acetaldehyde (177µl, 0.93mmol), dichloroethane (15ml) and *N,N*-dimethylformamide (2ml), was added sodium triacetoxyborohydride (197mg, 0.93mmol). After stirring overnight the reaction mixture was concentrated, dissolved in methanol and ethyl acetate and loaded onto an SCX-2 cartridge. The cartridge was washed with 0.2M ammonia in methanol solution, to provide 5-(5-{[[2-(*tert*-butyl-dimethyl-silanyloxy)-

ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (425mg) as a sticky solid. LCMS (Method B): R_T = 3.07 minutes; 513 $(M+H)^+$.

Intermediate 66: (similarly prepared to Intermediate 9, but using Intermediate 67)

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): R_T = 2.20 minutes; 468 $(M+H)^+$.

Intermediate 67: (similarly prepared to Intermediate 11, but using Intermediate 68)

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): R_T = 1.88 minutes; 369 $(M+H)^+$.

Intermediate 68:

(6-Bromo-pyridin-3-ylmethyl)-methyl-(2-phenoxy-ethyl)-amine

A solution of 2-bromo-pyridine-5-carbaldehyde (150mg, 0.81mmol) and 2-phenoxyethylamine (111mg, 0.81mmol) in dichloroethane (4.5ml) was stirred at room temperature for 7 hours. Sodium triacetoxyborohydride (433mg, 2.04mmol) and formaldehyde 37% w/w in water (340ml, 4.5mmol) were then added to the reaction mixture, which was stirred for a further 2 hours before being concentrated to provide a residue. The residue was dissolved in methanol and passed over a SCX-2 ion exchange cartridge using methanol followed by ammonia/methanol as eluent, to provide (6-bromo-pyridin-3-ylmethyl)-methyl-(2-phenoxy-ethyl)-amine (167mg) as a light brown oil. LCMS (Method B): R_T = 1.91 minutes; 321 & 323 $(M+H)^+$.

Intermediate 69: (similarly prepared to Intermediate 24, but using Intermediate 70)

{1-Oxy-6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 3.57 minutes; 570 $(M+H)^+$.

Intermediate 70: (similarly prepared to Intermediate 11, but using Intermediate 71)

5-(5-{[*tert*-Butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-1-oxy-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 3.47$ minutes; 471 $(M+H)^+$.

Intermediate 71:

(6-Bromo-1-oxy-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester

A solution of (6-bromo-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester (210mg, 0.52mmol, Intermediate 72) and *meta*-chloroperbenzoic acid (444mg, 1.56mmol) in dichloromethane (4ml) was stirred at reflux overnight. Saturated sodium hydrogen carbonate solution was then added and the mixture was stirred vigorously for 15 minutes. The aqueous phase was isolated and washed with dichloromethane (x2), then all the organic phases were combined, dried (Na_2SO_4) and concentrated, to provide (6-bromo-1-oxy-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester (quantitative) as a light brown oil. LCMS (Method B): $R_T = 3.38$ minutes; 423 & 425 $(M+H)^+$.

Intermediate 72:

(6-Bromo-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester

To a solution of (6-bromo-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-amine (826mg, 2.69mmol, Intermediate 73) and *N,N*-diisopropylethylamine (470μl, 2.7mmol) in dry dichloromethane (7ml) was added di-*tert*-butyldicarbonate (587mg, 2.69mmol). After stirring at room temperature for 1 hour the reaction mixture was concentrated to give a light brown viscous oil, which was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (gradient, 95:5 to 90:10v/v) as eluent, to provide (6-bromo-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-carbamic acid *tert*-butyl ester (885mg) as a light brown viscous oil. LCMS (Method B): $R_T = 4.21$ minutes; 407 & 409 $(M+H)^+$.

Intermediate 73:

(6-Bromo-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-amine

A solution of 2-bromo-pyridine-5-carbaldehyde (500mg, 2.69mmol) and 2-(phenoxy)-ethylamine (594mg, 4.3mmol) in anhydrous ethanol (14ml) was stirred at room temperature for 7 hours. Sodium borohydride (102mg, 2.7mmol) was then added to the solution, and the resultant mixture was allowed to stir for a further 3 hours before being quenched with water. The resultant mixture was concentrated, to provide (6-bromo-pyridin-3-ylmethyl)-(2-phenoxy-ethyl)-amine (quantitative), which was used without further purification. LCMS (Method B): R_T = 1.79 minutes; 307 & 309 $(M+H)^+$.

Intermediate 74: (similarly prepared to Intermediate 24, but using Intermediate 75)

{6-[5-(Tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-[2-(4-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.12 minutes; 622 $(M+H)^+$.

Intermediate 75: (similarly prepared to Intermediate 31, but using Intermediate 76)

5-[5-({*tert*-Butoxycarbonyl-[2-(4-trifluoromethyl-phenoxy)-ethyl]-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): R_T = 4.14 minutes; 523 $(M+H)^+$.

Intermediate 76: (similarly prepared to Intermediate 32, but using 4-trifluoromethylphenol)

(6-Bromo-pyridin-3-ylmethyl)-[2-(4-trifluoromethyl-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.45 minutes; 475 & 477 $(M+H)^+$.

Intermediate 77: (similarly prepared to Intermediate 24, but using Intermediate 78)

[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-{6-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-pyridin-3-ylmethyl}-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 3.88 minutes; 598 $(M+H)^+$.

Intermediate 78: (similarly prepared to Intermediate 31, but using Intermediate 79)

5-[5-({[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-*tert*-butoxycarbonyl-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): R_T = 3.77 minutes; 499 $(M+H)^+$.

Intermediate 79: (similarly prepared to Intermediate 32, but using 5-hydroxy-1,3-benzodioxole)

[2-(Benzo[1,3]dioxol-5-yloxy)-ethyl]-(6-bromo-pyridin-3-ylmethyl)-carbamic acid *tert*-butyl ester

LCMS (Method B): R_T = 4.08 minutes; 451 & 453 $(M+H)^+$.

Intermediate 80: (similarly prepared to Intermediate 9, but using Intermediate 81)

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): R_T = 2.19 minutes; 469 $(M+H)^+$.

Intermediate 81:

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid

To a solution of 5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid methyl ester (80mg, 0.21mmol, Intermediate 82) in methanol (4ml) was added 2M potassium hydroxide solution (2ml), and the resultant mixture was heated to 55°C. After stirring for 2 hours the mixture was acidified to pH 4 with concentrated hydrochloric acid then concentrated, to provide 5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid as a residue, which was used without further purification. LCMS (Method B): R_T = 2.03 minutes; 370 $(M+H)^+$.

Intermediate 82:

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid methyl ester

A stirred solution of [2-(5-bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-methyl-(2-phenoxy-ethyl)-amine (182mg, 0.45mmol, Intermediate 83), palladium (II) acetate (18mg, 0.08mmol), 1,3-bis(diphenylphosphino)propane (33mg, 0.08mmol), triethylamine (240µl, 1.6mmol), dry *N,N*-dimethylformamide (5.5ml) and methanol (4ml) was heated at 70°C under a 10 Barr carbon monoxide atmosphere. The reaction mixture was stirred overnight before being quenched with saturated sodium hydrogen carbonate solution. The resultant mixture was extracted with ethyl acetate (x2), and the organic layers were combined, washed with brine, dried (Na_2SO_4), then concentrated to provide a residue. The residue was heated in hot methanol from which a brown solid precipitated on cooling. The brown solid was collected by filtration and washed with diethyl ether, to provide 5-(4-{[*tert*-butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid methyl ester (85mg) as a solid. LCMS (Method B): R_T = 2.32 minutes; 384 $(M+H)^+$.

Intermediate 83: (similarly prepared to Intermediate 68, but using Intermediate 56 and 2-phenoxyethylamine)

[2-(5-Bromo-thiophen-2-yl)-pyrimidin-5-ylmethyl]-methyl-(2-phenoxy-ethyl)-amine

LCMS (Method B): R_T = 2.50 minutes; 404 & 406 $(M+H)^+$.

Intermediate 84: (similarly prepared to Intermediate 24, but using Intermediate 85)

5-(5-{[Ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): R_T = 2.24 minutes; 482 $(M+H)^+$.

Intermediate 85:

5-(5-{[Ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

To a stirred solution of 5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (660mg, 1.66mmol, Intermediate 86), in anhydrous tetrahydrofuran (10ml) under a nitrogen atmosphere was added potassium trimethylsilanolate (1.27g, 9.96mmol). The reaction mixture was stirred for 1 hour, then water was added and the resulting solution was adjusted to pH 5. The solution was extracted with ethyl acetate (x2) and the organic layers were isolated, combined, dried ($MgSO_4$) and concentrated, to provide 5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (503mg) as a solid. LCMS (Method B): R_T = 2.11 minutes; 383 $(M+H)^+$.

Intermediate 86:

5-(5-{[Ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester

To a solution of 5-(5-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (882mg, 3.57mmol, Intermediate 87) and ethyl-(2-phenoxy-ethyl)-amine (590mg, 3.57mmol), in dichloroethane (25ml) and *N,N*-dimethylformamide (1.5ml), was added sodium triacetoxyborohydride (756mg, 3.57mmol). After stirring overnight the reaction mixture was partitioned between dichloromethane and water, then the organic layer was isolated, dried ($MgSO_4$) and concentrated to give a dark yellow oil. The oil was subjected to silica-gel column chromatography using a mixture of cyclohexane and ethyl acetate (90:10, v/v) as eluent, to provide 5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester as yellow solid, which was used directly without further purification. LCMS (Method B): $R_T = 2.37$ minutes; 397 $(M+H)^+$.

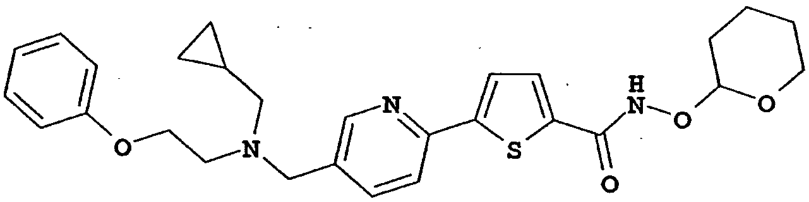
Intermediate 87:

5-(5-Formyl-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester

Diazomethane solution in diethyl ether (2M) (5.2ml, 10.4mmol) was added dropwise to a solution of 5-(5-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid (2.0g, 8.57mmol, Intermediate 16) in toluene (50ml). After stirring for 1 hour the reaction mixture was concentrated, to provide 5-(5-formyl-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester (2.07g) as a tan solid, which was used directly without further purification. LCMS (Method B): $R_T = 3.21$ minutes; 248 $(M+H)^+$.

Intermediate 88: (similarly prepared to Intermediate 24, but using Intermediate 89)

5-(5-{[Cyclopropylmethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide



LCMS (Method B): $R_T = 2.35$ minutes; 508 $(M+H)^+$.

Intermediate 89: (similarly prepared to Intermediate 85, but using Intermediate 90)

5-(5-{[Cyclopropylmethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 2.24$ minutes; 409 $(M+H)^+$.

Intermediate 90: (similarly prepared to Intermediate 86, but using *N*-cyclopropylmethyl-(2-phenoxy-ethyl)-amine)

5-(5-{[Cyclopropylmethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester

LCMS (Method B): $R_T = 2.49$ minutes; 423 $(M+H)^+$.

Intermediate 91: (similarly prepared to Intermediate 24, but using Intermediate 92)

5-(5-{[[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): $R_T = 3.14$ minutes; 612 $(M+H)^+$.

Intermediate 92:

5-(5-{[[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

To a solution of 5-{5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid (300mg, 0.84mmol, Intermediate 15) and (*tert*-butyldimethylsilyloxy)acetaldehyde (177µl, 0.93mmol) in dichloroethane (4.5ml) and *N,N*-dimethylformamide (1ml) was added sodium triacetoxyborohydride (197mg, 0.93mmol). The reaction mixture was heated at 55°C overnight, then concentrated to give a residue. The residue was dissolved in methanol and ethyl acetate and passed over a SCX-2 ion exchange cartridge which was washed using ammonia/methanol as eluent, to provide 5-(5-{[[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (425mg) as a sticky soild. LCMS (Method B): $R_T = 3.06$ minutes; 513 $(M+H)^+$.

Intermediate 93: (similarly prepared to Intermediate 24, but using Intermediate 94)

5-[5-({[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-phenethyl-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): $R_T = 3.01$ minutes; 596 $(M+H)^+$.

Intermediate 94: (similarly prepared to Intermediate 85, but using Intermediate 95)

5-[5-({[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-phenethyl-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 2.95$ minutes; 497 $(M+H)^+$.

Intermediate 95: (similarly prepared to Intermediate 86, but using Intermediate 96 and (*tert*-butyldimethylsilyloxy)acetaldehyde)

5-[5-({[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-phenethyl-amino}-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid methyl ester

LCMS (Method B): $R_T = 3.25$ minutes; 511 $(M+H)^+$.

Intermediate 96: (similarly prepared to Intermediate 10, but using Intermediate 87)

5-[5-(Phenethylamino-methyl)-pyridin-2-yl]-thiophene-2-carboxylic acid methyl ester

LCMS (Method B): $R_T = 2.25$ minutes; 353 $(M+H)^+$.

Intermediate 97: (similarly prepared to Intermediate 24, but using Intermediate 98)

(2-Phenoxy-ethyl)-[2-[5-(tetrahydro-pyran-2-yloxycarbamoyl)-thiophen-2-yl]-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazol-4-ylmethyl]-carbamic acid *tert*-butyl ester

LCMS (Method B): $R_T = 4.37$ minutes; 673 $(M+H)^+$.

Intermediate 98: (similarly prepared to Intermediate 85, but using Intermediate 99)

5-[5-{[*tert*-Butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 4.26$ minutes; 574 $(M+H)^+$.

Intermediate 99: (similarly prepared to Intermediate 72, but using Intermediate 100)

5-[5-{[*tert*-Butoxycarbonyl-(2-phenoxy-ethyl)-amino]-methyl}-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester

LCMS (Method B): $R_T = 4.94$ minutes; 602 $(M+H)^+$.

Intermediate 100: (similarly prepared to Intermediate 73, but using Intermediate 101)

5-[5-[(2-Phenoxy-ethylamino)-methyl]-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester

LCMS (Method B): $R_T = 2.80$ minutes; 502 $(M+H)^+$.

Intermediate 101:

5-[5-Formyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester

To a solution of 5-[1-(2-trimethylsilanyl-ethoxymethyl)-5-vinyl-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (45mg, 0.119mmol, Intermediate 102) in tetrahydrofuran (1.5ml) and water (1.5ml) was added a 4wt% aqueous solution of osmium tetraoxide (38μl, 5.95μmol), followed by sodium meta-periodate (51mg, 0.24mmol). The resultant reaction mixture was stirred at room temperature for 18 hours before saturated sodium hydrogen carbonate solution was added. The resultant mixture was extracted with dichloromethane (3x), and the organic layers were combined and then dried (Na_2SO_4), and concentrated under reduced pressure to give a residue. The residue was subjected to silica-gel column chromatography using a mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate (90:10, v/v) as eluent, to provide 5-[5-formyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (27mg) as an amber oil. LCMS (Method B): $R_T = 4.36$ minutes; 381 $(M+H)^+$.

Intermediate 102:

5-[1-(2-Trimethylsilanyl-ethoxymethyl)-5-vinyl-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester

A degassed solution of 5-[5-bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (100mg, 0.232mmol, Intermediate 103) in anhydrous toluene (5ml) was treated with tributylvinyl tin (170ml, 0.557mmol). The resulting solution was heated to 80^{O}C for 18 hours, before being treated with a 5M aqueous potassium fluoride solution (10ml) and stirred vigorously for 15 minutes. The organic layer was isolated and the aqueous layer extracted with dichloromethane (3x). The organic layers were combined and washed with brine, dried (Na_2SO_4) and concentrated to provide a residue, which was subjected to silica-gel column chromatography using a mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate (95:5, v/v) as eluent, to provide 5-[1-(2-

trimethylsilanyl-ethoxymethyl)-5-vinyl-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (50mg). LCMS (Method B): $R_T = 4.29$ minutes; 379 $(M+H)^+$.,

Intermediate 103:

5-[5-Bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester

A solution of 5-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (1.0g, 2.83mmol, Intermediate 104) in dichloromethane (25ml) was treated with *N*-bromosuccinimide (51mg, 0.284mmol). After stirring for 1 hour the reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution and brine. The organic layer was isolated, dried (Na_2SO_4) and concentrated to provide a residue, which was subjected to silica-gel column chromatography using a mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate (90:10, v/v) as eluent, to provide 5-[5-bromo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (1.02g). LCMS (Method B): $R_T = 4.61$ minutes; 431 & 433 $(M+H)^+$.

Intermediate 104:

5-[1-(2-Trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester

A degassed solution of 2-iodo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole (4.0g, 12.3mmol) in anhydrous tetrahydrofuran (50ml) was treated with 5-ethoxycarbonyl-2-thienylzinc bromide (24.7ml, 12.3mmol), followed by tetrakis (triphenyl-phospine)palladium (802mg, 0.62mmol). The resulting reaction mixture was heated to $80^{O}C$ for 2 hours, then concentrated under reduced pressure to give a residue. Water was added to the residue, which was extracted with ethyl acetate (3x). The combined organic layers were washed with water, then brine, dried (Na_2SO_4) and concentrated to give a residue, which was subjected to silica-gel column chromatography using a mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate (gradient, 90:10 to 80:20 v/v) as eluent, to provide 5-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-thiophene-2-carboxylic acid ethyl ester (1.5g). LCMS (Method B): $R_T = 3.72$ minutes; 353 $(M+H)^+$.

Intermediate 105: (similarly prepared to Intermediate 24, but using Intermediate 106)

5-{1-[2-(2-Phenoxy-ethoxy)-ethyl]-1*H*-imidazol-4-yl}-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

LCMS (Method B): $R_T = 2.67$ minutes; 458 $(M+H)^+$.

Intermediate 106: (similarly prepared to Intermediate 85, but using Intermediate 107)

5-{1-[2-(2-Phenoxy-ethoxy)-ethyl]-1*H*-imidazol-4-yl}-thiophene-2-carboxylic acid

LCMS (Method B): $R_T = 2.48$ minutes; 359 $(M+H)^+$.

Intermediate 107: (similarly prepared to Intermediate 5, but using Intermediate 108)

5-{1-[2-(2-Phenoxy-ethoxy)-ethyl]-1*H*-imidazol-4-yl}-thiophene-2-carboxylic acid ethyl ester

LCMS (Method B): $R_T = 3.21$ minutes; 387 $(M+H)^+$.

Intermediate 108:

5-(1*H*-Imidazol-4-yl)-thiophene-2-carboxylic acid ethyl ester

A solution of 5-(1-trityl-1*H*-imidazol-4-yl)-thiophene-2-carboxylic acid ethyl ester (7.82g, 16.83mmol, Intermediate 109) in dichloromethane (350ml) was treated with trifluoroacetic acid (21ml). After stirring for 1 hour the reaction mixture was cautiously treated with saturated sodium hydrogen carbonate solution. The resultant mixture was extracted with ethyl acetate (3x), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to provide a residue, which was subjected to silica-gel column chromatography using a mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate (gradient, 90:10 to 80:20, v/v) as eluent, to provide 5-(1*H*-imidazol-4-yl)-thiophene-2-carboxylic acid ethyl ester (3.02g). LCMS (Method B): $R_T = 1.90$ minutes; 223 $(M+H)^+$.

Intermediate 109: (similarly prepared to Intermediate 104, but using 4-iodo-1-trityl-1*H*-imidazole)

5-(1-Trityl-1*H*-imidazol-4-yl)-thiophene-2-carboxylic acid ethyl ester

LCMS (Method B): $R_T = 4.52$ minutes; 465 $(M+H)^+$.

Intermediate 110:

5-(5-{[Benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide

A solution of 5-(5-{[benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (180mg, 0.49mmol, Intermediate 111) in *N,N*-dimethylformamide (7ml) was treated with *N,N*-diisopropylethylamine (170µl, 0.98mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (57mg, 0.49mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (186mg, 0.49mmol). The mixture was stirred at room temperature for 1 hour, then diluted with water, and extracted with ethyl acetate (3x). The organic layers were combined, washed with saturated sodium hydrogen carbonate solution, brine, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue. The residue was dissolved in methanol and passed over a SCX-2 ion exchange cartridge using methanol followed by ammonia/methanol as eluent, to provide 5-(5-{[benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide (192mg) as a brown sticky gum. LCMS (Method B): R_T = 2.07 minutes; 468 $(M+H)^+$.

Intermediate 111: (similarly prepared to Intermediate 85, but using Intermediate 112)

5-(5-{[Benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid

LCMS (Method B): R_T = 1.92 minutes; 369 $(M+H)^+$.

Intermediate 112: (similarly prepared to Intermediate 86, but using Intermediate 87 and 2-hydroxyethyl benzylamine)

5-(5-{[Benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid methyl ester

LCMS (Method B): R_T = 2.27 minutes; 383 $(M+H)^+$.

Intermediate 113:

5-(5-{[Methyl-(2-phenoxy-ethyl)-amino]-methyl}-1*H*-imidazol-2-yl)-thiophene-2-carboxylic acid methyl ester

A stirred solution of [2-(5-bromo-thiophen-2-yl)-3*H*-imidazol-4-ylmethyl]-methyl-(2-phenoxy-ethyl)-amine (0.36g, 0.93mmol, Intermediate 114), palladium (II) acetate (38mg, 0.167mmol), 1,3-bis(diphenylphosphino)propane (69mg, 0.167mmol), triethylamine (325μl, 2.33mmol), dry *N,N*-dimethylformamide (15ml) and methanol (10ml) was heated at 70^{O}C under a 20 Barr carbon monoxide atmosphere overnight. After allowing to cool, the reaction mixture was concentrated and subjected to reverse-phase preparative HPLC using acetonitrile and water (gradient 20:80 to 40:60, v/v, over 30 minutes), to provide 5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-1*H*-imidazol-2-yl)-thiophene-2-carboxylic acid methyl ester (90mg) as a pale yellow oil. LCMS (Method B): R_T = 2.10 minutes; 372 $(M+H)^+$.

Intermediate 114:

[2-(5-Bromo-thiophen-2-yl)-3*H*-imidazol-4-ylmethyl]-methyl-(2-phenoxy-ethyl)-amine

A solution of [2-(5-bromo-thiophen-2-yl)-3*H*-imidazol-4-yl]-methanol (250mg, 0.97mmol, Intermediate 115) in thionyl chloride (5ml) was heated at 80^{O}C for 10 minutes, before being allowed to cool. The reaction mixture was evaporated to dryness to give a residue, which was dissolved in anhydrous chloroform and concentrated to provide a solid foam. The foam was redissolved in chloroform (10ml) to which 2-(phenoxy)-ethylamine (160μl, 0.97mmol) was added, followed by anhydrous triethylamine (4ml). The reaction mixture was stirred at room temperature for 30 minutes, before 1N sodium hydroxide solution was added. The organic layer was separated, and the aqueous layer extracted with chloroform (2x). The combined organic extracts were dried ($MgSO_4$) and concentrated, to provide [2-(5-bromo-thiophen-2-yl)-3*H*-imidazol-4-ylmethyl]-methyl-(2-phenoxy-ethyl)-amine (433mg) as a brown oil. LCMS (Method B): R_T = 2.29 minutes; 392 & 394 $(M+H)^+$.

Intermediate 115:

[2-(5-Bromo-thiophen-2-yl)-3*H*-imidazol-4-yl]-methanol

To a solution of 5-bromo-thiophene-2-carboxamidine (2.5g, 10.35mmol, Intermediate 116) in 25% aqueous ammonium hydroxide (25ml), was added 1,3-dihydroxyacetone dimer (1.86g, 10.35mmol). The reaction mixture was heated at 80^{O}C for 40 minutes, before being allowed to cool, and then extracted with ethyl acetate. The remaining aqueous layer was extracted with ethyl acetate, and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an oily solid. The oily solid was triturated with diethyl ether, to provide [2-(5-bromo-thiophen-2-yl)-3*H*-imidazol-4-yl]-methanol (1.38g) as a buff solid. LCMS (Method B): R_T = 1.37 minutes; 259 & 261 $(M+H)^+$.

Intermediate 116:

5-Bromo-thiophene-2-carboxamidine

Ammonia gas was bubbled through a cooled ($0^{O}C$) solution of ethanol (150ml) for 25 minutes. 5-bromo-thiophene-2-carboximidic acid ethyl ester (31g, 0.11mol) in ethanol (200ml) was added portionwise to the cooled ($0^{O}C$) solution of ammonia in ethanol maintaining the reaction mixture temperature below $10^{O}C$. The solution was allowed to warm to room temperature and stirred for a further 6 days with ammonia gas being bubbled through for 1 hour on each of the first two days. The reaction mixture was then evaporated to dryness to give a residue, which was triturated with diethyl ether, to provide 5-bromo-thiophene-2-carboxamidine (25.91g) as a white solid. LCMS (Method B): R_T = 0.66 minutes; 205 & 207 $(M+H)^+$.

Intermediate 117:

5-Bromo-thiophene-2-carboximidic acid ethyl ester

A cooled ($-10^{O}C$) solution of 5-bromo-thiophene-2-carbonitrile (32.5g, 0.17mol) in ethanol (250ml) was stirred whilst gaseous hydrochloric acid was bubbled through for 1.5 hours. After stirring for a further 2 hours the reaction mixture was left to stand overnight, before being evaporated to dryness to provide a residue. The residue was triturated with diethyl ether, to provide 5-bromo-thiophene-2-carboximidic acid ethyl ester (41g) as a white solid. LCMS (Method B): R_T = 1.96 minutes; 234 & 236 $(M+H)^+$.

Biological Activity

Compounds are tested for their capacity to inhibit histone deacetylase activity (primary assay) and for their biological effects on growing cells (secondary assay).

Deacetylase Assay

Total lysates from K562 chronic human myelogenous leukemia cells (obtained from American Type Culture Collection, Rockville, MD) are used as source of HDAC activity. Cells are grown in RPMI media supplied with 10% FCS, harvested by centrifugation, washed once in PBS and resuspended at a density of 24×10^6/ml in HDA buffer (15mM Potassium phosphate pH 7.5, 5% glycerol, 0.2mM EDTA). After sonication, lysates are centrifuged at 1000*g* for 20 minutes and the resulting supernatant is aliquoted and stored at –80°C. Alternatively, commercially available HeLa nuclear extracts (BIOMOL) are used as source of histone deacetylase activity.

The assay was carried out for 30 minutes using 116μM of a fluorescent substrate containing an acetylated lysine residue (BIOMOL). When deacetylation of the lysine occurs, the substrate can react with the added developer producing a fluorophore. The amount of fluorophore produced is proportional to the HDAC activity in the sample and is quantified using a multiwell fluorimeter capable of excitation at 360nm and detection at 450nm.

Compounds are diluted in DMSO prior to addition to assay buffer, the final DMSO concentration in the assay being 1%.

The percent activity of the compounds in reducing histone deacetylase enzymatic activity is calculated as follow:

$$\% \text{ activity} = \{ (F^S - B) / (F^C - B) \} \times 100$$

where:

F^S is the fluorescence at 450nm in the presence of the tested compound (Sample).
F^C is the fluorescence at 450nm in the presence of vehicle 1 % DMSO (Control).
B is the fluorescence at 450nm in the absence of enzyme (Background fluorescence)

The IC_{50} is defined as the concentration at which a given compound achieves 50% activity. IC_{50} values are calculated using the XLfit software package (version 2.0.5).

Secondary Assay

Compounds are tested in a cell proliferation assay using the following cell lines:

MCF-7	human mammary gland adenocarcinoma (ATCC)
MDA-MB-231	human mammary gland adenocarcinoma (ATCC)

Both cell lines are free of *Mycoplasma* contamination (PCR Mycoplasma Detection Set, Takara). MCF-7 are kept in MEM medium (Gibco) supplemented with 10% FCS and 1% Non Essential Amino Acids at 37°C in a 5% CO_2 humidified incubator. MDA-MB-231 are kept in L-15 (Leibovitz) medium (Gibco) supplemented with 15% FCS at 37°C in a non-modified atmosphere, humidified incubator.

Cells are seeded in 96-well plates at a density of 20,000 cells/ml (3,000 cells/well) and after 24h they are exposed to different concentrations of compounds in 0.1% DMSO. Cells are grown for a further 72h, the media is removed and the cells are frozen at –80°C for at least 30 minutes and lysed in a solution containing the CyQUANT dye. This is a fluorescent molecule that specifically binds nucleic acids and whose fluorescence is greatly enhanced upon binding nucleic acids. Therefore the fluorescence intensity is proportional to the number of cells present in each well and can be quantified using a multiwell fluorimeter by measuring the fluorescence of the solution at 520nm.

The percent activity of the compounds in reducing cell number is calculated as follow:

$$\% \text{ activity} = \{ (A^S - B) / (A^C - B) \} \times 100$$

where:

A^S is the fluorescence at 520nm in the presence of the tested compound (Sample).

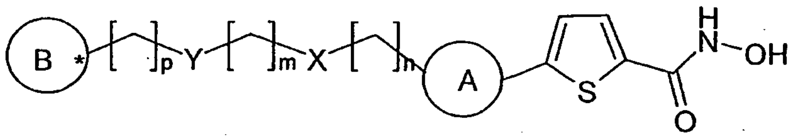
A^C is the fluorescence at 520nm in the presence of vehicle 0.1% DMSO (Control).

B is the fluorescence at 520nm in the absence of cells (Background fluorescence).

The IC_{50} is defined as the concentration at which a given compound achieves 50% activity. IC_{50} values are calculated using the XLfit software package (version 2.0.5).

CLAIMS

1. A compound of formula (I):



(I)

in which

A represents optionally substituted monocyclic heteroaryl or phenyl

B represents optionally substituted heteroaryl, aryl, aryl-fused-heterocycloalkyl, heteroaryl-fused-cycloalkyl, heteroaryl-fused-heterocycloalkyl or aryl-fused-cycloalkyl

X and Y, which may be the same or different, each independently represent -O-, -NR^1-, -CO-, -SO_2-, -SO-, -S-, -NR^1CO-, -NR^1SO_2-, -CONR^1-, -SO_2NR^1-, -NR^1CONR^1-
or X may be a direct bond when Y represents -NR^1-, -NR^1CO-, -NR^1SO_2-, -CONR^1-, -SO_2NR^1- or -NR^1CONR^1- provided that R^1 represents alkyl substituted by -OR^2, -NR^3R^4, -NR^4COR^5, -$NR^4SO_2R^5$, -$CONR^3R^4$ or -$SO_2NR^3R^4$

R^1 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, or alkyl substituted by -OR^2, -NR^3R^4, -NR^4COR^5, -$NR^4SO_2R^5$, -$CONR^3R^4$ or -$SO_2NR^3R^4$

R^2 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl

R^3 represents H or alkyl

R^4 represents H, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocycloalkyl or cycloalkyl

or NR^3R^4 represents a cyclic amine

R^5 represents alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl

n represents 0-3
m represents 1-3
p represents 0-3

and corresponding *N*-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compounds.

2. A compound according to claim 1 wherein A is a monocyclic heteroaryl group, containing 5 or 6 ring atoms and wherein the heteroatom(s) is/are selected from N, O and S atoms.

3. A compound according to claim 1 or 2 wherein said A group is a monocyclic heteroaryl group wherein the heteroatom(s) are N atom(s).

4. A compound according to claim 1, 2 or 3 wherein said A group contains one or two ring heteroatoms.

5. A compound according to claim 1 wherein A is optionally substituted pyridinyl, pyrazolyl, imidazolyl or pyrimidinyl.

6. A compound according to any preceding claim wherein X is selected from -O- and $-NR^1-$.

7. A compound according to any preceding claim wherein Y is selected from -O- and $-NR^1-$.

8. A compound according to claim 1, 6 or 7 wherein R^1 is selected from H, alkyl and alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$.

9. A compound according to claim 1, 6 or 7 wherein R^1 is selected from alkyl substituted by $-OR^2$ or NR^3R^4.

10. A compound according to claim 1, 8 or 9 wherein R^2 is H or alkyl.

11. A compound according to claim 1, 8 or 9 wherein R^3 and R^4 are independently selected from H and alkyl.

12. A compound according to claim 1, 6 or 7 wherein R^1 is selected from arylalkyl, heteroarylalkyl, heterocycloalkylalkyl and cycloalkylalkyl.

13. A compound according to any preceding claim wherein X is selected from -O- and -NH-.

14. A compound according to any preceding claim wherein Y is selected from -O-

15. A compound according to claim 1 wherein Y is NR^1, X is a direct bond and R^1 is alkyl substituted by $-OR^2$, $-NR^3R^4$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^3R^4$ or $-SO_2NR^3R^4$.

16. A compound according to any preceding claim wherein the group B is selected from aryl and aryl-fused-heterocycloalkyl.

17. A compound according to any preceding claim wherein n is 0, 1 or 2.

18. A compound according to any preceding claim wherein m is 2 or 3.

19. A compound according to any preceding claim wherein p is 0, 1 or 2.

20. A compound according to claim 1 wherein A represents pyridinyl, n represents 0 or 1, X represents -NR^1-, m represents 2 or 3, Y represents -O- and p represents 0 or 1.

21. A compound according to claim 1 wherein A represents pyrazolyl, n represents 2, X represents -O-, m represents 2, Y represents -O- and p represents 0 or 1.

22. A compound according to claim 1 wherein A represents imidazolyl.

23. A compound according to claim 1 selected from:

5-[5-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide;

5-{1-[2-(2-phenoxy-ethoxy)-ethyl]-1*H*-pyrazol-3-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(6-{[3-(3-acetylamino-phenoxy)-propylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(6-{[benzyl-(2-dimethylamino-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-[6-(2-benzyloxy-ethylamino)-pyridin-2-yl]-thiophene-2-carboxylic acid hydroxyamide;

5-{6-[(2-phenoxy-ethylamino)-methyl]-pyridin-3-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(3-trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(4-methoxy-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2-chloro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(4-fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(3-methoxy-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(3-fluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2,6-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2,5-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2,6-dichloro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(2,4-difluoro-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{5-[(2-phenoxy-ethylamino)-methyl]-pyrimidin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(1-{2-[benzo[1,3]dioxol-5-ylmethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1*H*-pyrazol-3-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[(2-hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{1-oxy-5-[(2-phenoxy-ethylamino)-methyl]-pyridin-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(4-trifluoromethyl-phenoxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[2-(benzo[1,3]dioxol-5-yloxy)-ethylamino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-pyrimidin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[ethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[cyclopropylmethyl-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[(2-hydroxy-ethyl)-(2-phenoxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[(2-hydroxy-ethyl)-phenethyl-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide;

5-{5-[(2-phenoxy-ethylamino)-methyl]-1*H*-imidazol-2-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-{1-[2-(2-phenoxy-ethoxy)-ethyl]-1*H*-imidazol-4-yl}-thiophene-2-carboxylic acid hydroxyamide;

5-(5-{[benzyl-(2-hydroxy-ethyl)-amino]-methyl}-pyridin-2-yl)-thiophene-2-carboxylic acid hydroxyamide; and

5-(5-{[methyl-(2-phenoxy-ethyl)-amino]-methyl}-1*H*-imidazol-2-yl)-thiophene-2-carboxylic acid hydroxyamide.

24. A compound according to any of claims 1 to 23, for use in therapy.

25. The use of a compound according to any of claims 1 to 23 in the manufacture of a medicament for the treatment of a disease in which inhibition of histone deacetylase can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease.

26. A method for treating a disease in a patient in which inhibition of histone deacetylase can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the patient a therapeutically effective amount of a compound according to any of claims 1 to 23.

27. A method or use according to claim 25 or 26 wherein said disease is a disease caused by increased cell proliferation.

28. A method or use according to claim 25 or 26 wherein said disease is cancer, psoriasis, fibroproliferative disorders, smooth muscle cell proliferation disorders,

inflammatory diseases and conditions treatable by immune modulation, neurodegenerative disorders, diseases involving angiogenesis, fungal and parasitic infections and haematopoietic disorders.

29. A method or use according to claim 25 or 26 wherein said disease is liver fibrosis, arteriosclerosis, restenosis, rheumatoid arthritis, autoimmune diabetes, lupus, allergies, Huntington's disease, retinal diseases, protozoal infections, anaemia, sickle cell anaemia and thalassemia.

30. A method or use according to claim 29 wherein said protozoal infection is malaria, toxoplasmosis or coccidiosis.

31. A method or use according to claim 29 wherein said retinal disease is diabetic retinopathy, age-related macular degeneration, interstitial keratitis or rubeotic glaucoma.

32. A method or use according to claim 25 or 26 wherein said disease is congestive heart failure due to hypertrophy of cardiac myocytes.

33. A method or use according to claim 25 or 26 wherein said condition is premature parturition caused by decreased progesterone receptor activity.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB2004/000353

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/04 A61K31/38 A61P35/00 C07D409/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/26696 A (ROMERO MARTIN MARIA ROSARIO ;FINN PAUL W (GB); HARRIS C JOHN (GB);) 4 April 2002 (2002-04-04) example 189 ---	1,24-26
E	WO 2004/013130 A (ARGENTA DISCOVERY LTD ;PRICE STEPHEN (GB); BORDOGNA WALTER (GB); D) 12 February 2004 (2004-02-12) examples -----	1-33

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 15 April 2004	Date of mailing of the international search report 03/05/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer De Jong, B

INTERNATIONAL SEARCH REPORT

In ... nal Application No
PCT/GB2004/000353

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0226696	A	04-04-2002	AU	9013401	A	08-04-2002
			CA	2423868	A1	04-04-2002
			EP	1335898	A1	20-08-2003
			WO	0226696	A1	04-04-2002
WO 2004013130	A	12-02-2004	WO	2004013130	A1	12-02-2004

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/GB2004/000353

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.